Joint DOE/NSF Report of the Workshop on: Biological Information Processing and Systems

Co-Chairs: **James J. Hickman**[1]
Larry Dooley[2]

Held on: January 19-20, 2001

The first workshop for the materials division at DOE and the second in a series of NSF workshops to establish the current state-of-the-art in biological computation and future directions in this exciting new field.

Report Date: January 31, 2002

Sponsors:
Council on Energy Engineering Research
Experimental and Integrative Activities Division and Computer and Information Science and Engineering Directorate/National Science Foundation

EXECUTIVE SUMMARY

[1] Workshop Co-Chair; Advisor to the Division Director, NSF/CISE/EIA; Hunter Endowed Chair of Biomaterials, Department of Bioengineering, Clemson University
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The second level of abstraction in biological information technology and the enabling tools for building artificial neuronal systems were two of the major highlights from the joint DOE and NSF workshop on Biological Information Processing and Systems. The workshop brought together the leading researchers and funding managers in the emerging field of biological computation. This workshop highlighted current cutting-edge basic and applied research going on in this area. A central goal of biological computation research is to understand how biological systems "compute": what tasks are being carried out by nervous systems, what are the algorithms with which those tasks are being executed, and what is the functional architecture of the biological systems through which those algorithms are implemented. Although work in this area is of considerable intrinsic interest and importance from the "basic research" standpoint, the specific focus of this workshop was to consider the application of that knowledge toward the development of enabling tools for building artificial neuronal systems. Specifically, how might knowledge about biological computation aid the development of the next generation of information technology; from standpoints of algorithms *and* hardware?

The workshop focused on three main topics: *In Silico* Systems, Multi-cellular Information Processing, and Constructing Hybrid systems. Keynote addresses were given by Drs. Frederica Darema and Gary Strong from the NSF. The *In Silico* session featured presentations on single-cell modeling from a number of viewpoints; most notably the engineering approach to modeling cellular information processing encoding (Stephanopolous) *vs.* the genetic or pathway approach to information processing (Brent). These presentations inspired a lively debate on the issues. The second session focused on mechanisms through which neuronal ensembles process information, and presented insights gained from biological systems ranging from the simple invertebrate motor networks (lobster digestive system (Abarbanel)) to more complex vertebrate sensory systems (auditory processing in birds). Participants also summarized how neuronal ensembles may be interfaced directly with silicon devices and then be used to control devices without our full understanding of the underlying computational processes (Ditto). A key talk in the second session on multi-cellular information processing featured ground-breaking work from Miller's lab at Montana State, that demonstrated a novel approach for deciphering the information encoded in the activity patterns of nerve cells. Coupled with Abarbanel's work on information processing modeling based on a 14-neuron motor-control system in the lobster, Miller's results strongly suggest how information might be encoded and decoded at various processing stages of simple nervous systems. This now leads the way for the community to develop theories for computational processing at this "network" level, and concurrently to experimentally verify this next level of abstraction in biological systems. The discussion following these presentations focused primarily on the implications of that research, and there was universal excitement from the participants because of the synergy of the two research programs.

The third session featured talks on how to construct hybrid neuronal systems, and on how to interface such biological systems to non-biological (primarily silicon) systems. This involves the creation of tools and rules for building simple systems of neurons by treating them as "components" in the same sense that electrical engineers can construct devices from resistors, capacitors, transistors, and the host of other opto-electronic

components (Egert, Hickman, and Wheeler). The work has now progressed to the point that building neuronal systems with a defined number of neurons, with a defined number of synaptic connections, and interfacing these directly with silicon, is realizable in the near future.

A grand challenge will be to interface synthetic systems to isolated subsystems of the brain (Berger) and even to the intact brain (Anderson). Anderson's work was especially intriguing, because he and his colleagues are attempting to interface synthetic motor control systems *not* to the brain's primary motor control area, but instead to the area of the brain called the *parietal cortex* where the *intent* of motor movements are manifest. Thus, the target for the movement of a prosthetic (or robotic) arm would be determined by reading out the intended movement vector directly at a high, pre-motor level, rather than through deciphering the complex set of motor-level commands generated to control the multitude of limb muscles during a reaching movement. This part of the workshop contained the most discussion, as many had not realized the research had progressed this far, and since the implications of the type of systems neuroscientists could build appeared to be limitless. It was concluded that even the concept of creating systems comprised of 3-5 neurons with defined synapses in specific locations could advance the field order of magnitude beyond its present capabilities.

In summary, the workshop illustrated the cutting edge research, from studies of information processing in single cells to studies of much more complex systems in the primate brain. The workshop also illustrated very effectively the experimental verification of the next level of abstraction in neuronal systems, and demonstrated how the biological hardware can be assembled in such systems for experimental verification of existing theoretical models or for the development of new theories. Finally, results and tools were presented that demonstrated how to construct hybrid neuronal systems from the simple to the complex and interface them directly to silicon-based systems.

SCHEDULE

BIOLOGICAL INFORMATION PROCESSING AND SYSTEMS WORKSHOP

Friday, January 19, 2001
Bell South Auditorium - Madren Conference Center

12:00 – 1:00 PM	**Registration** – Lobby, Madren Center
1:00 – 1:30 PM	**Welcome and Introduction** Bob Price (DOE) Rick Adrion (NSF) James J. Hickman (Clemson and NSF)
1:30 – 2:15 PM	Ed Uberbacher (Oak Ridge National Laboratory) " Protein Structure Predictors And The Role Of Protein Complexes In Cellular Information Processing"
2:15 – 2:40 PM	**Session I: *In Silico* Systems: From Experiment to Simulation** *Discussion Leader* - Laura Landweber (Princeton) Roger Brent (Institute for Molecular Science) "Information Processing by Cells and Biologists"
2:40 – 3:10 PM	**Break**
3:10 – 4:00 PM	**Session I continued** Gregory Stephanopoulos (MIT), "A Platform Of Flux And Gene Expression Measurements For Metabolic Engineering And Drug Discovery" James I. Garrels (Proteome, Inc.), "A Knowledge Resource For The Post-Genomic Era: Turning Information Buried In The Scientific Literature Into Readily-Accessible Knowledge"
4:00 – 5:30 PM	**Discussion**
6:00 – 7:45 PM	**Dinner** – Ballroom A
8:00 – 9:30 PM	**Keynote Addresses**: Bell South Auditorium Introduction – Kwabena Boahen (University of Pennsylvania) Frederica Darema (NSF), "Synergistic Approaches for Creating Neurobiologically Inspired Computing Systems" Gary Strong (NSF), "Information: The Language of Biology"
9:30 PM	**Reception** – Lobby, Madren Center

Saturday, January 20, 2001

Bell South Auditorium - Madren Conference Center

7:30 – 8:15 AM	**Continental breakfast** – Lobby, Madren Center
8:15 – 9:00 AM	Ulrich Egert (Albert-Ludwigs University), "'Brains' on Chips – Neurobiology from Basic to Applied Science"
9:00 – 9:50 AM	**Session 2: Multi-cellular Information Processing** *Discussion Leader* - J. Barhen (Oak Ridge National Laboratory) Todd Troyer (Maryland) "Information Processing in Cortical Circuits: Temporal Multiplexing and the search for the Conical Microcircuit" Henry D. I. Abarbanel (University of California, San Diego), "Biological Neurons, Electronic Neurons, Neural Information Processing"
9:50 – 10:10 AM	**Break**
10:10 – 11:00 AM	**Session 2 continued** John Miller (Montana State University), "Analysis Of Neural Encoding In Sensory Systems: Progress And Barriers" William Ditto (Georgia Institute of Technology), "Exploiting Neural Tissue: From Algorithms to Animats"
11:00 – 12:15 PM	**Discussion**
12:15 – 1:15 PM	**Lunch** – Lobby and Breakout Rooms
1:15 – 2:05 PM	**Session 3: Constructing Hybrid Systems** *Discussion Leader* - Bruce Wheeler (UICU) Andreas Offenhaeusser (University of Mainz), "Electrical cell signals measured by field-effect transistors" J. Hickman (Clemson University) "Constructing Simple Hybrid Neuronal Devices"
2:05 –2:15 PM	**Break**
2:15 – 3:05 PM	**Session 3 continued** Theodore Berger (University of Southern California), "Neurobiological Neural Nonlinear Dynamics for Temporal Pattern Recognition: Biologically Realistic Neural Networks for Signal Processing and Neural Prosthetics" Richard Anderson (Cal Tech) "Using the Posterior Parietal Cortex for a Neural Prosthesis"
3:05 – 4:20 PM	**Discussion**
4:20 – 4:45 PM	**Break**
4:45 – 6:00 PM	**Reports from session chairs & discussion; Adjourn**
6:30 - ?	Informal gathering at a local establishment

WORKSHOP SESSION REPORTS

Discussion and presentations of the workshop focused on three areas: *in silico* systems, multi-cellular information processing and constructing hybrid systems.

SESSION 1: *In Silico* Systems: From Experiment to Simulation

Moderator: Laura Landweber, Princeton University

As may be expected from such a session, the talks by Roger Brent (Molecular Sciences Institute), Gregory Stephanopoulos (MIT), and James Garrels (Proteome, Inc.) raised more questions than answers, including the following:

- What is the appropriate level to model?
- What aspects of the biological systems are predictive?
- Is something effectively being computed, and if so, *what*?
- Is the appropriate computational model *digital* or *analog* (or sometimes both)?
- Are biological switches and regulatory networks effectively like *state machines*, complete with stable attractors and chaotic regimes (Kauffman, in Endy & Brent 2001), and would "control theory" therefore be useful?
- Is there further a use for coding theory or information theory, and at what level? Or, do we need a *new theory* to treat biological ensembles?

An audience participant even brought up the comparison between classical and quantum mechanics. Dr. Brent added that we need a "theory about how coarsely you need to sample (e.g. 'importance sampling')."

Both Dr. Brent and Dr. Stephanopoulos asked whether specific parts of a cell – 'subroutines' of proteins and ligands – are comparable to a *wire*, an *integrator*, a *gate*, or some other aspect of computer hardware? Lila Kari compared this challenge to "the revenge of Plato"— that we should suddenly and abruptly be trying to describe in mathematical terms the entire natural world that we study. But, they acknowledged, we cannot turn to philosophy, or metaphysics, for concrete advice. The careful biologist must go back and forth tuning parameters (such as *priors*, the biological initial conditions) and equations in a theoretical model to data from lab experiments.

Bacterial chemotaxis, though not explicitly discussed in this session, offers a success story in this realm (as demonstrated by the work of Stanislas Leibler and others at Princeton University). HIV dynamics (Alan Perelson at Santa Fe Institute and Los Alamos National Laboratory, Martin Novak at The Institute for Advanced Study, and colleagues) is another, where predictive behaviors have emerged and have impacted both basic and applied research.

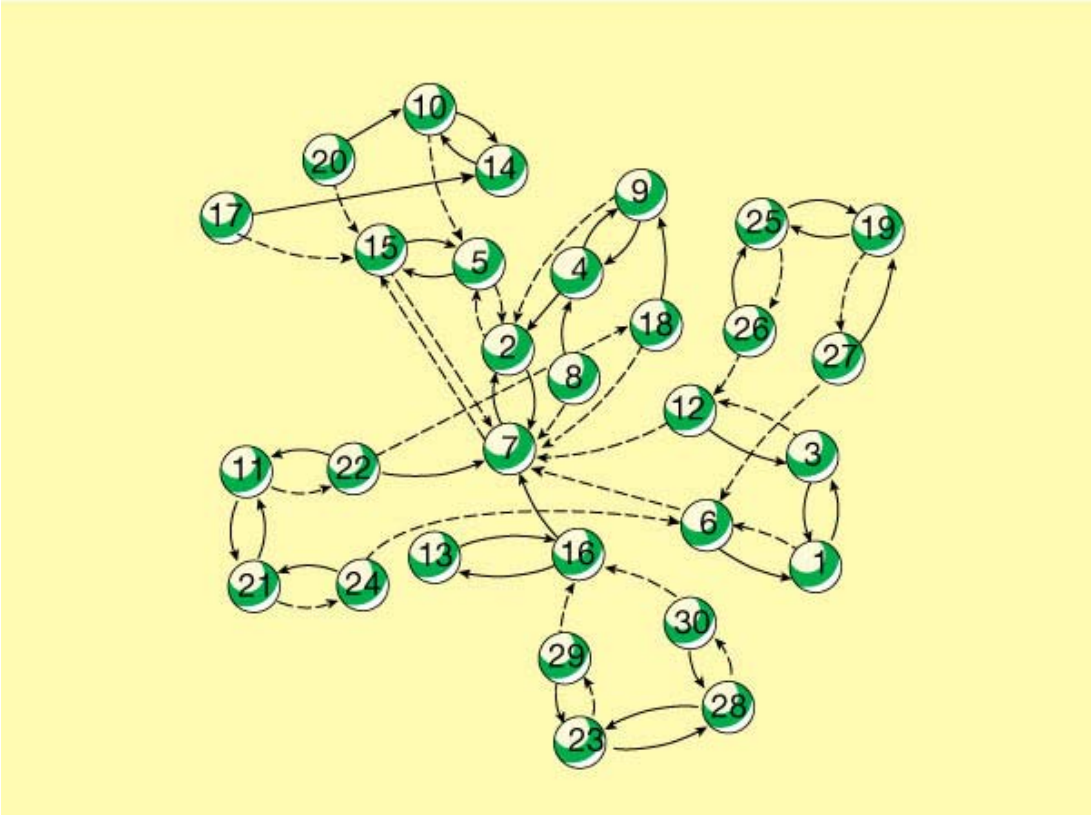
Still, very few researchers either focus on one such data-rich model-friendly system and/or go the distance to meld theory and experimental data so thoughtfully. Wistfully, the audience offered neurobiology as a paradigm, where information theory and application of other quantitative tools have really delivered insight, and as a system inherently more amenable to mathematical modeling than the workings of a single-cell.

Another question explored during this session was how much data are enough to model? Despite the fact that we appear to be in an information-rich, coming-of-age era of biological data with new genome sequences filling our hard-drives every month, this is just a small fraction of the entire picture, the *zeroth layer*. A sequence itself is a qualitative piece of information and is one-dimensional. Gene expression, localization data, and accompanying RNA and protein structures are qualitative and quantitative additions to this first dimension. The bioliterature and

annotation business, like Dr. Garrels' company Proteome, Inc. appears to be doing superbly on a grand scale. Individual researchers (e.g. Steve Benner's lab in Florida) are developing on a much smaller, but also useful scale, a tool to navigate the first layer. The website www.proteome.com offers functional information and interactions, and also links to all the orthologs and paralogs in the database, when available, at least for other model organisms.

The next level of intricate diagrams of regulatory networks, like intermediary metabolism, is itself a two-dimensional *qualitative* simplification, or summary of our understanding of complex cellular phenomena. We know very little about robustness and sensitivity to perturbations in most cases (whether genetic, metabolic, or environmental change). Information about enzyme kinetics *in vivo* (including subtle nuances like local metal ion concentrations), enzyme localization, as well as enzyme regulatory mechanisms, is required to construct quantitative models for cellular processes, themselves the behavior of chemical ensembles in low diffusion environments.

Figure 1. Representation of a genetic regulatory network. There are 30 stable states in this

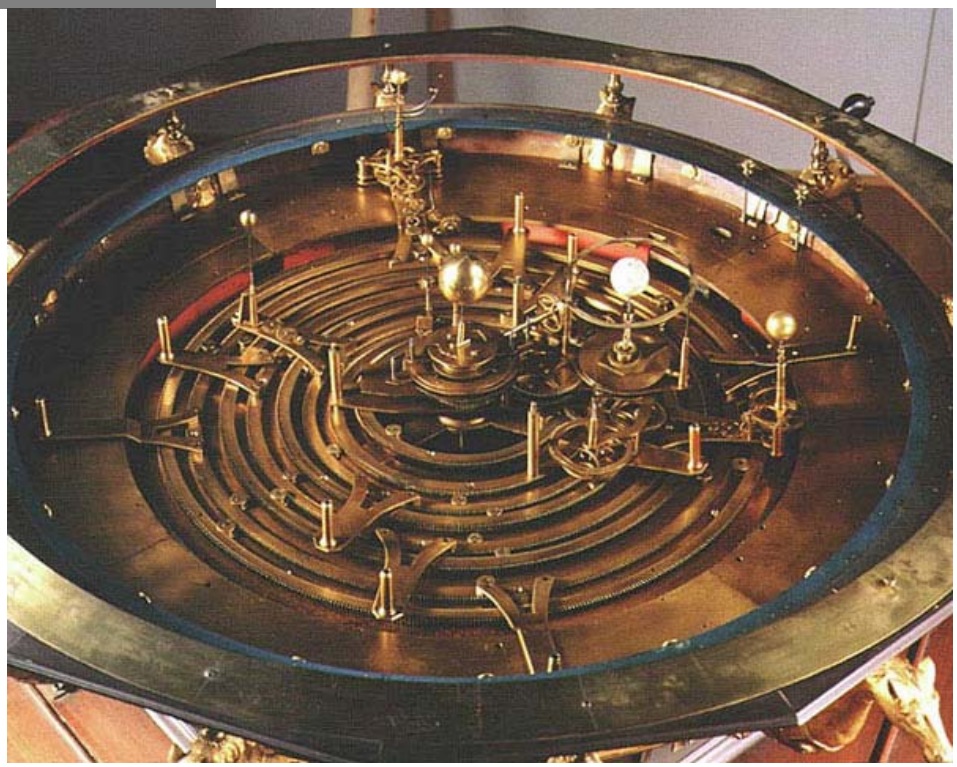


Metabolic engineering, like biological modeling or computing (nebulous terms, meant here to embrace both the quantitative descriptions of biological behavior and the *uses* of biological components to construct computational devices), requires a vast, even if incomplete, understanding of the toolbox and wiring in a single cell to be able to divert its processes to some other defined or improved goal.

Chemical engineers including Dr. Stephanopoulos, and the community of biochemists and molecular biologists, including Dr. Bent as well as quantitative scientists who want to make use of or plunder the molecular data, have a tremendous need for organized information and resources, to navigate even the calm seas of static data (sequences, expression levels,

localization, sensitivity, etc.), let alone to begin to wade into the nostromo of the biological dynamics of a single cell.

Figure 2. Mechanical simulation of classical mechanics in 1773.
The 'Grand Orrery' computes the positions of planets and moons in the Solar System. Subsequent models in the next century were able to *predict* the existence and approximate location of Neptune (from Endy & Brent *Nature* 18 Jan 2001).



Recommendations

The following recommendations were offered:

1) Support better ways to model. New math, algorithms, importation of appropriate theoretical concepts (e.g. control theory, theory about how coarsely you to sample (e.g. "importance sampling"), theory about how to compose simulations from different levels of abstraction) from other forums where complex things have been simulated successfully, such as weapons work. It is important to note that more quantitative education across disciplines is needed for biologists, and in general.

2) Support open source code sharing.

3) Support challenge problems.

4) Support evaluation forums ala CASP.

5) Support better ways for biologists to construct (by pointing and clicking), visualize, and interact with simulations.

6) Support better ways for making single cell measurements and population measurements.

7) Support making databases "friendlier" to quantitative modeling.

8) Support making representations of qualitative biological knowledge that are computable.

9) Support hybrid qualitative / quantitative representations.

10) Help import tools from other communities, including mathematical and algorithmic insights, concepts, and techniques for analysis of signals, and any insights that go beyond analysis of the signal to an understanding of its substituent symbols and of its meaning.

During discussion, it was learned that NSF will make efforts to insist that co-Principal Investigators on multi-disciplinary grants be respected by their universities and their respective departments. It was noted that it should be easy for co-PI's to be from different departments and that status and respect often correlate roughly with money. Also, NSF plans to take the lead on discussions with universities about "quality control" guidelines that will help universities evaluate younger investigators involved in multidisciplinary research.

(For additional information from the session see the Session Notes on page 26.)

SESSION 2: Multi-cellular Information Processing

Moderator: J. Barhen, Oak Ridge National Laboratory

Presentations delivered by Todd Troyer (Maryland), Henry Abarbanel (University of California, San Diego), John Miller and William Ditto (Georgia Institute of Technology) explored information processing in terms of coding schemes, neuron classification, encoding and utilization of neural tissue. Encoding and the factors (especially technological factors) that influence progress of obtaining knowledge in neuroscience were discussed by Dr. Miller (Figure 3).

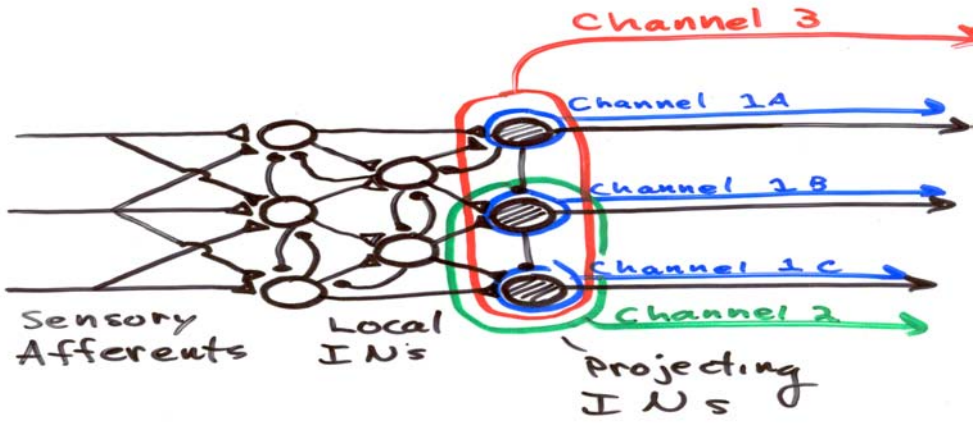


Figure 3. Experimental and theoretical neuroscientists typically assume that the correlate of an information channel or processing unit is a single neuron, and neural "circuit diagrams" are usually drawn with each "component" being a single neuron (e.g., the black circles in this figure). The mapping of "channels" and / or "processors" onto nerve cell networks may be more complex, in several respects. E.g., several independent channels of information might be

multiplexed across different subsets of the three projecting interneurons in this schematic circuit diagram . (Courtesy of J. Miller, University of Montana)

In order to identify the factors and determine whether they may be barriers to progress, Dr. Miller suggested that it is necessary to first consider the theoretical context in which neural systems are studied. He asked, "What is the mapping between the functional architecture and the biological architecture?" For example, if Information Theory is an appropriate framework for the analysis of neural systems, then:

- What is the correlate of an "information channel" within a nervous system?
- What is the nature of the "neural code?"
- Is information multiplexed over the channels?

Further, there may be other analytical frameworks that are more appropriate for other more central processing stages within nervous systems (e.g., non-linear control theory).

Abarbanel presented work to look at the hardware that is used to encode the information and the information transport in biological systems. He used "channels" of Electronic Neurons (ENs) coupled with analog circuit synapses and computer synapses (dynamic clamp) to explore information transport in neural circuits. He focused on using the neuron that controls the lobster digestion system (Figure 4) to understand how information received by sensory systems from the environment is transported to muscles for action and to brains for decisions. His analog circuit ENs quantitatively replaced a biological neuron removed from the Pyloric Central Pattern Generator and restored the natural rhythm of the biological circuit (Figure 5).

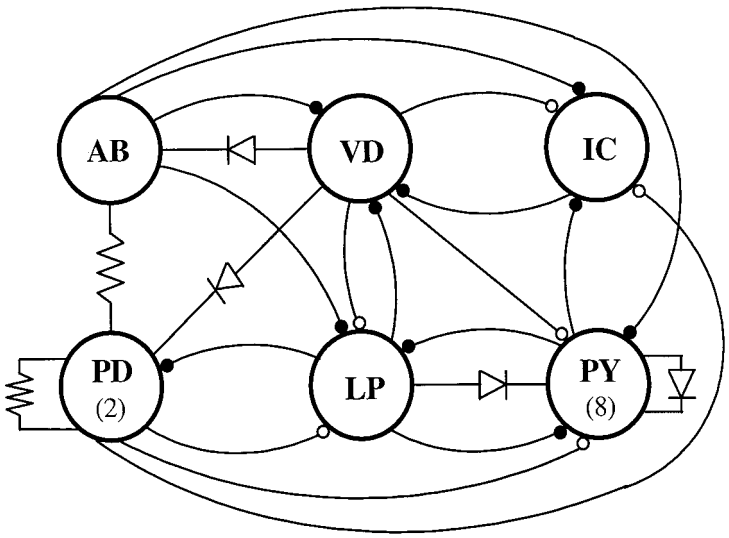


Figure 4. Observed connectivity in the lobster control network; Pyloric Central Pattern Generator. (Courtesy of H. Abarbanal, UCSD)

He addressed the questions:

- How is information encoded during this communication process?
- How is it decoded at functional locations?
- How can we reliably study this issue in laboratory biological preparations?
- How can we use ENs to address this set of biological questions in a realistic, believable way?
- How can we use the lessons for new strategies in signal processing or control…; i.e. new forms of computing, realized in silicon, based on biological examples?

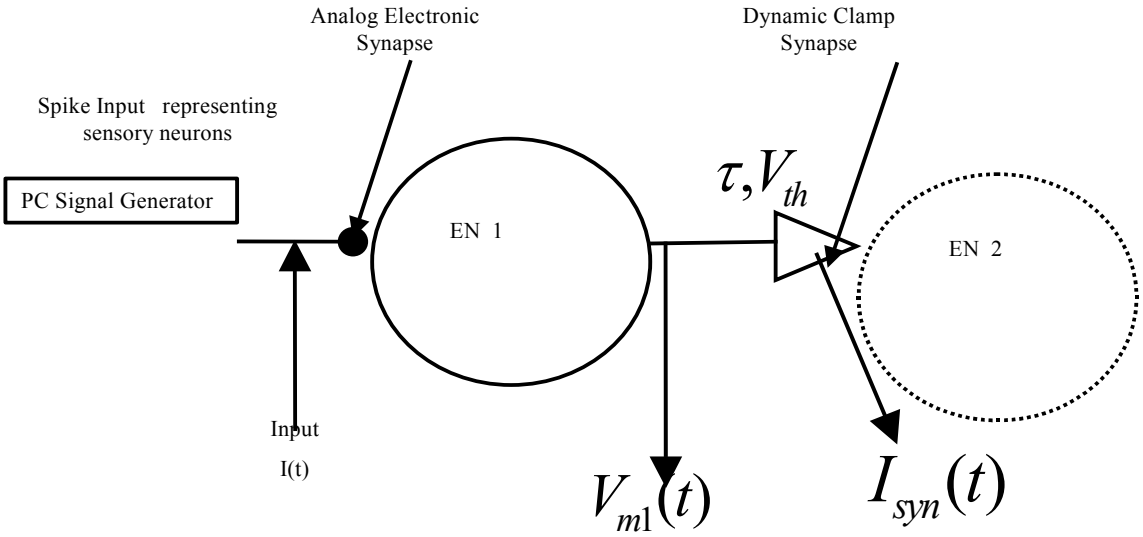


Figure 5. Theoretical process for encoding and decoding neuronal information as it is transported down a process and through the cell body. (Courtesy of H. Abarbanal, UCSD)

The largest technological barriers that affect progress were identified. Recording presents several challenges. There is difficulty recording (1) from nerve cells reliably and with long-term stability and (2) from large numbers of nerve cells simultaneously. Once a reading is made, it is difficult to discriminate activity of individual cells from multiunit records. Further, there is the need for a way to decipher neural "symbols," in the sense of Shannon's Information Theory, from raw neural signals. We need to interact with the system in real time. Also, experiments, theory and modeling should be integrated more effectively, more essentially and seamlessly. Lastly, neuroscientists need more data from experiments that are designed to test alternate experimental hypotheses.

Recommendations and Needs

1) Long-term biological-electrical interfaces

2) Means to design and fabricate hybrid (biological and synthetic) circuits.

3) Algorithms, software and hardware tools for massive data stream acquisition.

4) Algorithms, software and hardware tools for on-line interactive signal processing for –
   a. data reduction (e.g. spike discrimination)
   b. "information" analysis
   c. interactive control

5) Multi-dimensional graphical user interfaces for the tools listed in items 3 and 4 above.

6) Enabling interdisciplinary collaboration is equally essential for achieving progress. The cooperation and contributions of neuroscientists, computer scientists, electrical and computer engineers, mathematicians and physicists are needed.

(For additional information from the session, see Session Notes on page 36.)

SESSION 3: Construction of Hybrid Systems

Moderator: Bruce C. Wheeler, University of Illinois at Champaign-Urbana

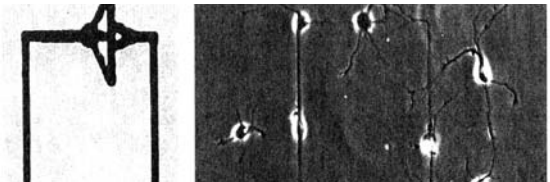
The presentations and discussions addressed three common themes in this session: Observational Tools, Modeling Tools, and Experimental Design. The talks included those by: Andreas Offenhauesser (Electrical Cell Signals Measured by Field Effect Transistors); James J. Hickman (Constructing Simple Hybrid Neuronal Devices); Theodore Berger (Neurobiological Nonlinear Dynamics for Temporal Pattern Recognition), and Richard Andersen (Using the Posterior Parietal Cortex for a Neural Prosthesis). Short presentations were given by: Nitish Thakor (Neuro-Chemical Information Processing); Sacha Nelson (Multi-unitary Synaptic Inputs); and Eberhard Voit (Biochemical Systems Theory). The lead talk by Ulrich Egert ("Brains on Chips - Neurobiology from Basic to Applied Science) was directly relevant to this theme.

There is substantial overlap in the ideas and consensus of sessions 2 and 3. The greatest interest in the talks of this session was prompted by consideration of experimental design, taken loosely to include approaches to basic science questions, to prosthetic design, and to biosensors and drug screening assays. There was consensus that the role of the observational and modeling tools was to assist in the more efficient design of quality experimentation.

Presentations were given with respect to three different levels of experimental observation: channel- and other subcellular-level activity (Offenauesser); cellular-level as measured by spiking activity (all speakers); and multi-cellular, as measured by field potential activity (Berger, Andersen). Each approach has its strengths.

Offenhauessers' presentation described the use of substrate electrodes with patch recording properties in detecting individual ion channel currents. This approach may be promising for providing insight into intracellular pathways and signaling. Hickman and Offenhauesser (and Wheeler in opening remarks; also Berger) provided details of approaches for designing neural networks in culture, including precise placement of neurons in patterns (Figure 6) and on electrodes, control of polarity (directional growth of axons vs. dendrites, Figure 7 (Hickman)), functional connectivity, and multielectrode recordability (Figure 8).

The technology of patterning cultured neurons onto electrode surfaces, shows promise but is at an early stage. As a consequence, there remains considerable uncertainty as to the experimental paradigms that ultimately will emerge to provide definitive insight into neural computation. Nonetheless, there was strong confirmation that small, reliable, robust, designable networks have substantial value as tools for basic neuroscience information processing and eventually mainstream computer science. Berger strongly supported the concept that even a two-neuron circuit in which the synaptic connections were known had great value to efforts to find realistic models of synaptic function. This notion was supported by the general audience. It is notable that Berger already has a synaptic learning model of great promise to speech recognition and other temporal information coding problems. In general it is understood that the imposition of designable and repeatable order or structure to *in vitro* neural networks is of great potential value for furthering our understanding of how neural networks perform biological computation. The more robust and complex the networks, the more sophisticated will be the nature of the answerable neurocomputation questions. Further applications lie in biosensors and in drug screening.



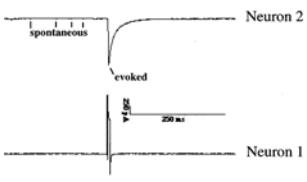


Figure 6. Neuronal circuit pattern utilizing hippocampal E18 neurons in serum-free media after 7 days in culture. With electrophysiological recordings at 12 days from the hippocampal neurons on the unpatterned control (top, right) and patterned neurons (bottom, right), indicating functional synapses in both cases. (From Ravenscroft, et al., *JACS,* 1998.)

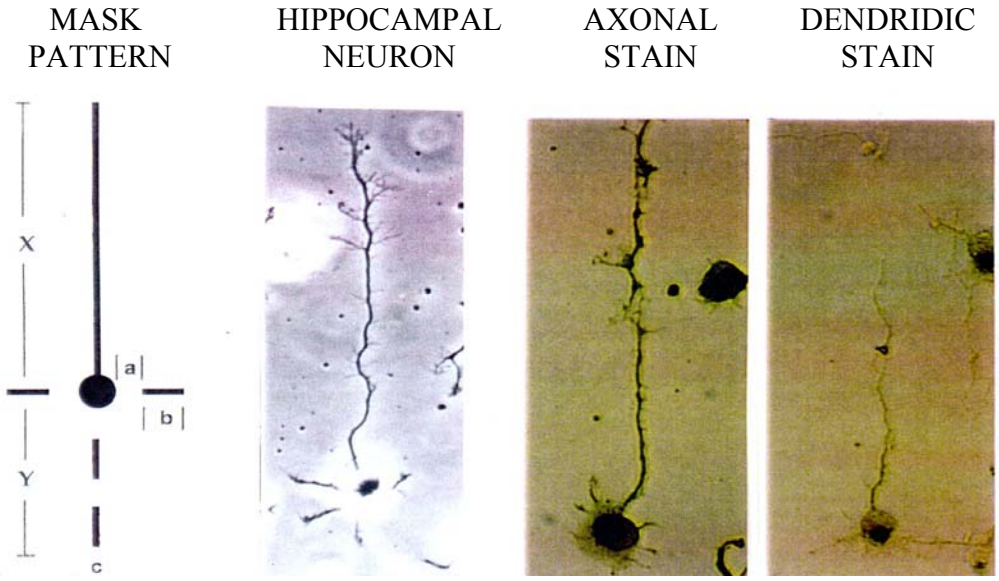


Figure 7. Directional axonal outgrowth from hippocampal neurons by geometric surface manipulation and the inducement of polarity. (From Stenger, et al., *Neuroscience Methods*, 1998.)

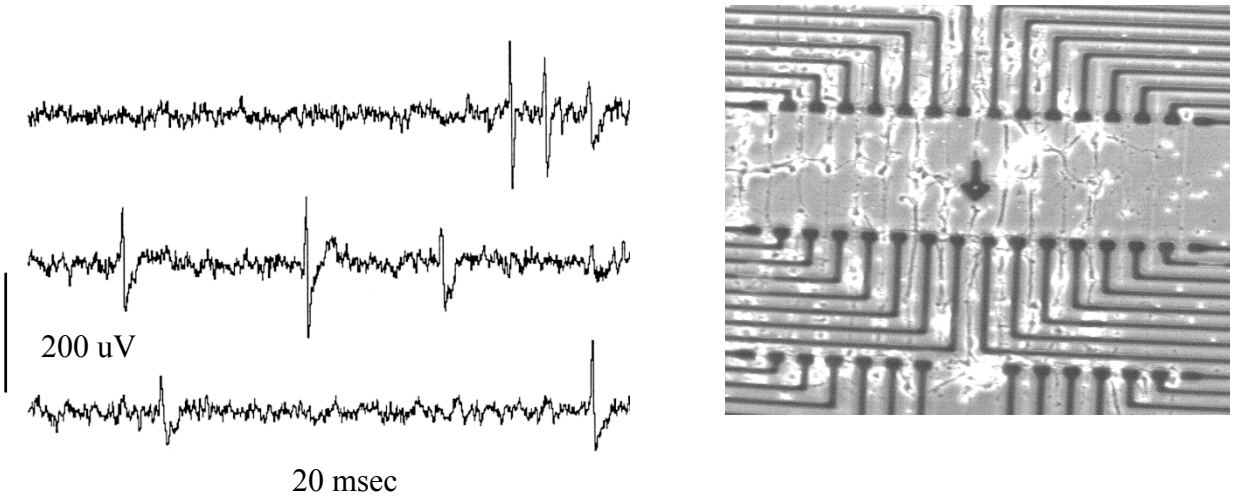


Figure 8. Long-term electrical recording and patterning from hippocampal neurons on a microelectrode array (right) with action potentials from multiple sites on this array (left). (Courtesy of Bruce Wheeler, University of Illinois at Champaign-Urbana.)

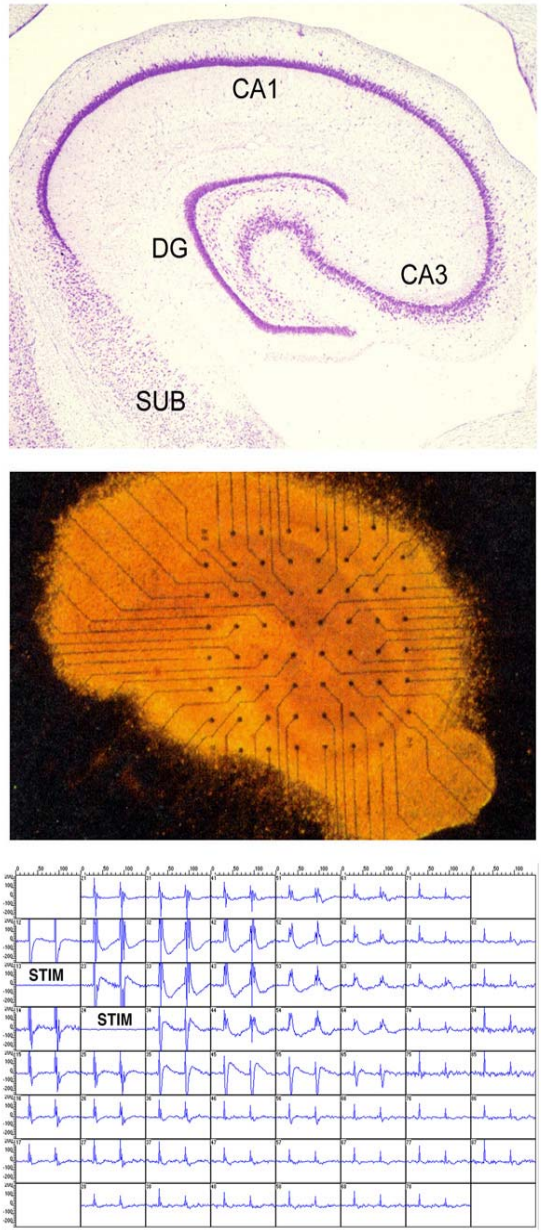


Figure 9. Top panel: Cresyl violet-stained cross-section of the hippocampus showing its major subregions -- dentate gyrus (DG), CA3, CA1, and subiculum (SUB). Middle panel: Photomicrograph of a hippocampal slice culture prepared on the surface of a multi-site electrode array (from MEA). Bottom panel: Example multi-site recording of extracellular field potentials evoked throughout hippocampus in response to electrical stimulation of hippocampal afferents.

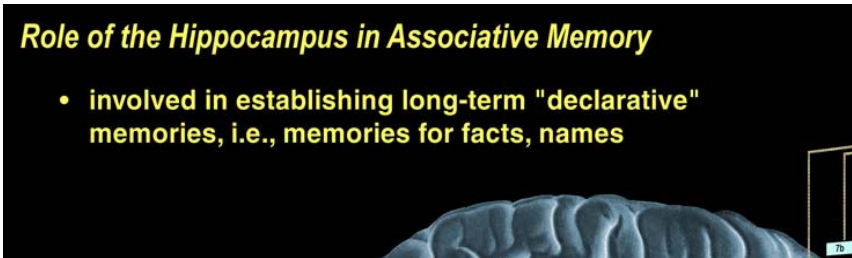


Figure 10. Center: Location of the hippocampus relative the rest of the human brain. Right: Diagrammatic representation of the hierarchical organization of the visual system (from Van Essen), as an example of one of the several sensory systems that ultimately provides input to hippocampus (bottom of diagram: retina; top of diagram: hippocampus). Each box in the hierarchical structure represents one subcomponent of the visual system responsible for extracting a particular class of features.

Prosthetics provide the most compelling short-term justification for hybrid neural systems. The most successful prosthetic to date is the cochlear implant. Presented at the workshop was a blueprint for a prosthesis in which a robotic arm would be controlled by signals from the parietal reach region of cortex both for the onset of movement intent as well as the direction of the movement (Andersen). The demands of the prosthesis provide a high priority need for well-constructed designs, albeit ones that are challenging to implement. Neural prosthetics in the future clearly will expand into the realm of biomimetic devices that interface, not with sensory or motor components of the nervous system, but instead with central brain regions, e.g., cognitive prosthesis to replace hippocampal function (Figures 9 and 10 (Berger)).

Observational Tools

There has been substantial progress in the development of multiple element electrode arrays (Offenhauesser, Hickman, Berger, Thakor, Egert). FETs have been incorporated into substrates and can be used routinely (Offenhauesser). There have been reports of success with substantial flows of multichannel data (Egert, Berger). Hence, there was considerable optimism made. Examples are the information theoretic approaches mentioned by several speakers in other sessions; non-linear analyses (Berger and other's). There was mixed opinion as to the immediate need for novel modeling approaches. The exceptions lay in two areas: data compression
techniques for dealing with large volumes of multidimensional data; and better understanding of what models/techniques scale with greater dimension and complexity.

Recommendations and Needs

1) Support for better observational tools
2) Support for better dissemination of modeling and data analysis tools
3) Support for well-designed experiments interfacing neural tissue with computational, information, and recording devices.
4) Support for the development of technology for designable, patterned networks of neurons.

(For additional information from the session, see Session Notes on page 38.)

Prospects

Biological systems are complex assemblies tuned through evolutionary forces to accomplish tasks. They either accomplish these tasks or fail, so what we observe are systems that work. This hardly means they work in an "**optimal**" or "**best**" fashion from any engineering or mathematical point of view. A lesson of this workshop was that nonetheless there are critical lessons one may take away from the study of biological systems which imply directly or indirectly innovative designs for future computations: algorithm execution, sensing, information processing,…

No one suggested slavishly reproducing biological solutions to computing issues, however informative that might be, but a focus on uncovering and then using the **biological design principles** to solve interesting problems, and to do it at frequencies and scales relevant to the problems posed. New sensors which process environmental information, for example, might be based on how the honey bee olfactory system works, but using the honey-bee design one would develop a sensor tuned to the chemicals of interest, presented at the environmental time scales of interest, in a format of use to the user of the information---hopefully, one would then solve the computational problem: detect odor and report "bad" chemicals in a robust and sensitive fashion.

As one observer said, we are on the verge of gaining insights into neural computation which will be of use to computational scientists. The problems faced by nervous systems (and by neuroscientists) are very different from conventional computational problems. Progress to data is encouraging enough to bring computational scientists to look more attentively at these problems. Already the work of Berger appears promising in application to word recognition and perhaps other difficult pattern recognition problems.

We also appear to be on the verge of substantial progress in neuroprosthetic devices, a new class of models for basic neuroscience (designable patterned neural networks). There was hope that a creative industry/research relationships could be forged in the area of tools for neuroscience. One mechanism is the subsidy of equipment purchase to facilitate close industry/research interactions. This workshop clearly demonstrated that these general goals are realizable in a steady, well-focused research effort. It also presented numerous approaches to a practical implementation of such a research program.

ABSTRACTS

Protein Structure Predictors, Protein Complexes, and Networks in Cellular Information Processing

Ed Uberbacher
Computational Biology Section
Life Sciences Division
Oak Ridge National Laboratory

Abstract

Recent developments in computing and experimental techniques such as mass spectrometry are making it more realistic to comprehensively understand the proteins, protein structures, protein complexes and networks that facilitate cell processes. This talk will discuss some perspectives on types of cellular information, and approaches and some early progress toward whole proteome structure prediction, computational modeling of protein complexes, and automated computational derivation of cell processes. The methods described will include threading based structure prediction, high-throughput hybrid computational and experimental methods using mass spectrometry and NMR, extensions of hybrid mass spectrometry methods to protein complexes, and sequence comparative approaches to deriving integrated views of genome regulatory signals, regulatory networks, pathways. The context of this work within new initiatives in DOE and elsewhere will be described.

SESSION 1: *In Silico* Systems: From Experiment to Simulation

Information Processing by Cells and Biologists

Roger Brent
The Molecular Sciences Institute
Berkeley, California

Abstract

The core agenda of post-WWII molecular biology has been defined as the molecular understanding of how genetic information was transmitted and read out (see for example Stent 1968), and, by the 1950's, the analogy between the tape in a Turing machine and the linear sequence of nucleotides in DNA was apparent to both computer scientists and biologists.

In the early 21st century, I believe that molecular biology needs to return to these roots, and to recast part of its agenda in terms of the need to understand how biological information is processed. In a somewhat more modern formulation, cells can be thought of as machines that process and make decisions on three kinds of information: 1) information stored in the genome 2) information about intracellular events (for example from checkpoint mechanisms) and 3) information external to the cell.

In many cases the machinery that cells use to make decisions is reasonably well understood at a qualitative level. However, in no case do we possess a corresponding quantitative understanding, nor can we well-predict the outcomes of perturbations to the genome, the internal workings of the cell, or its external environment.

One path to understanding the behavior of these ensembles of components clearly lies in construction of mechanism-based quantitative models representing cellular processes. Building such models requires solution of numerous computational and experimental biological challenges, some of which are being dealt with by Drew Endy and Larry Lok, who are present at this meeting. I will detail some of these.

Another path may involve computation on the qualitative biological knowledge that now exists. Expert biologists reason on this qualitative information to make statements about the consequences of perturbations, but expert systems that do the same in the main do not exist. Here, although the need is clear, the relative opacity (to me) of much of the seemingly relevant computer science literature has made it more difficult to figure out first steps.

Finally, note that information theory (Shannon 1948) has it roots in the 20th century need to understand transmission of electrical signals through channels. It is not immediately clear that the representations of biological processes used by biologists map well to concepts that come from this theory. To give only one example, one is hard pressed to define or find, inside a cell that is processing signals from the outside, either the signal or the "bits" (Tukey, 1946) that might make it up. There may be thus be an opportunity here for new theory to guide thinking and further experiment.

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A Platform of Flux and Gene Expression Measurements for Metabolic Engineering and Drug Discovery

Gregory Stephanopoulos
Professor, Department of Chemical Engineering
MIT

Abstract

Metabolic engineering focuses on pathway modification to improve cellular properties. As such, it relies on intracellular measurements elucidating the control of flux in metabolic and signal transduction pathways. This talk will discuss challenges in intracellular flux measurements and genome-wide gene expression measurements using DNA microarrays from the perspective of metabolic engineering and drug discovery applications. Emphasis will be placed on *integration and quantification* as dominant underlying themes in systems biology where engineering can make major contributions. In this context, the linkage between metabolic (physiological) measures and expression phenotypes will be presented as a major challenge in post-genome bioengineering research.

A Knowledge Resource for the Post-Genomic Era: Turning Information Buried in the Scientific Literature into Readily-Accessible Knowledge

James I. Garrels
Proteome, Inc., Beverly, MA

Abstract

Proteome, Inc. carries out comprehensive literature curation to recast protein-based knowledge into a new Web-based format built on the framework of the genome. Our databases for yeast (YPD), worm (WormPD), and S. pombe (PombePD) represent complete curation of the literature for these organisms. Proteome is now deeply engaged in a large-scale effort to curate protein information for human, mouse, and rat. The combined product of all these databases is a unified knowledge resource known as the BioKnowledge Library. The resource contains tabulated protein information based on ontologies including the Gene Ontology system of Ashburner, and it also includes a large amount of more detailed information extracted from literature as indexed "bullet points". The system allows easy navigation between related proteins of the same or different species through sequence or pathway relationships, and all entries are tied to the original literature sources. The resource will be presented in the context of finding new ways to quickly access large amounts of gene- and protein-based knowledge in the post-genomic era.

EVENING SESSION

Synergistic Approaches for Creating Neurobiologically Inspired Computing Systems

Frederica Darema
Senior Science and Technology Advisor
NSF/CISE

Abstract

The presentation will discuss challenges and opportunities for research at the interface of Neurobiology and Computing intended to lead into new computing systems architectures and programming paradigms that will augment the current capabilities of the von-Neumann computing systems. The talk will address the need for tools to understand information processing in biological systems and the ways to emulate the biological processes. The interest is how to build systems rather than hybrid (bio/silical) devices. While developing hybrid device capabilities is a useful step, these capabilities are not sufficient to guide us in developing biologically inspired systems. Advances in this direction will need synergistic, multidisciplinary and collaborative research involving neurobiologists, computer scientists and engineers. The presentation will address research challenges and approaches as well as issues of managing multidisciplinary research initiatives leading to revolutionary and novel computing systems.

Information: The Language of Biology

Gary Strong
EIA/CISE/NSF

Abstract

Natural language processing (NLP) and biology share many characteristics, not least of which is a need to do data mining over massive amounts of data. NLP tools, such as hidden Markov models, have been among the best gene finders. Researchers are extracting protein-protein interaction networks from the scientific literature and are exploring protein grammars to predict functional properties from sequence. DARPA success in its natural language programs suggests important features for any Federal bioinformatics efforts: the critical need for annotation tools and standards, objective community wide evaluations, motivation by continual technology transfer, and important national challenge problems on which to focus.

'Brains' on Chips – Neurobiology from Basic to Applied Science

Ulrich Egert
Albert-Ludwigs University

Abstract

An increasing body of data collected in recent years indicates that the properties and the behavior of individual cells are dynamically modulated by the temporal and spatial structure of the embedding network. It is therefore necessary to evaluate manipulations of these cells, e.g. drug effects on a given neuron, in the context of the activity dynamics of the surrounding neuronal network. Understanding the interplay of cells within small, yet complex networks *in vitro* could thus improve the predictability of drug effects in the intact organism. Electrophysiological recording techniques suitable to monitor the activity of neuronal populations in multi-site recordings have recently become available. These multi-electrode tools record spike activity and low frequency potentials with substrate integrated electrodes at many sites in the tissue. They thus facilitate the collection of sample sizes necessary for statistical analysis. The possibility to electrically stimulate the tissue further expands the range of applications and bioassays.

For *in vitro* experiments microelectrode arrays (MEA) have been developed in which thin-film or silicon electrodes or FETs are integrated into the supporting substrate, avoiding the need for micromanipulators. Meanwhile, numerous preparations have been adapted to MEA recordings, ranging from acute brain slices, cultured neuronal tissues, to studies of circadian rhythms with recordings for many days. For example, we are developing an assay estimating the selectivity of dopaminergic drugs for D_2 and D_3 receptor subtypes in different cerebellar lobuli to facilitate these investigations during industrial drug screening and thus its throughout. Other projects investigate LFPs and spike activity in hippocampal slices, cerebellar tissue cultures and thalamocortical slices. I will give an overview of the techniques, our strategies for data analysis, and some of the in-vitro applications of MEA-recording established in our lab

SESSION 2: Multi-cellular Information Processing

Information Processing in Cortical Circuits: Temporal Multiplexing and the Search for the Canonical Microcircuit

Todd Troyer
University of Maryland

Abstract

One cubic millimeter of cortex contains approximately 40,000 neurons and a billion synapses, and each neuron receives input from on the order of 10,000 other neurons. Of necessity, understanding information processing in circuits of this complexity rely on simplifications and a focus on underlying principles. One common simplification is the assumption that neurons use some form of "rate code." This assumption is currently under intense scrutiny, with competing spike-based or "temporal codes" receiving much attention. While the rate code explanation has stood up quite well experimentally, the study of temporal signals is pushing the definition of "rate." The key question is likely not to be which coding scheme is present, but rather how multiple coding schemes are multiplexed in time. While it is common for theoreticians to focus on a relatively uniform population of neurons, one of the great outstanding problems in neuroscience is to understand the computational importance of the highly stereotyped connectivity between cortical layers that is repeated (with variation) throughout the neocortex. Improvements in patch clamp recording techniques, both in vitro and in vivo, as well as the increased use of multi-electrode recordings are generating a wealth of data. While theoretical progress is being made, general principles await discovery.

Biological Neurons, Electronic Neurons, Neural Information Processing

Henry D. I. Abarbanel
Department of Physics
and
Marine Physical Laboratory
Scripps Institution of Oceanography
University of California, San Diego

Abstract

Using methods of nonlinear time series analysis, we have determined that a class of invertebrate central pattern generator neurons exhibit chaotic bursting spiking membrane voltage activity expressing four degrees of freedom. Using these observations we have built analog electronic neurons (ENs) that capture these four degrees of freedom and are strikingly realistic in their interactions with each other and with biological neurons. We have replaced biological neurons in biological circuits with our ENs and shown that our ENs interact with each other in small networks just as biological neurons are observed to do. We will discuss these results and show how we can use these ENs to study biologically interesting questions focusing on information transport in neuronal networks. Other potential applications of ENs will be discussed.

Analysis Of Neural Encoding In Sensory Systems: Progress And Barriers

John P. Miller
Montana State University

Abstract

What are the nature of the encoding schemes through which information is encoded, processed and transmitted between different stages within nervous systems? What computational algorithms are operating within nervous systems? How are those algorithms mapped onto the architecture of the biological "wetware?" Can we discover fundamental aspects of neural encoding and transmission schemes which can be translated into practical engineering designs for advanced computational and communications systems? Answering these questions will require the development and application of new analytical approaches, and also the development of new tools for the acquisition and analysis of massive data streams.

I will review our recent work focused on the analysis of neural encoding and decoding in a simple sensory system. We have used analytical approaches from information theory to study ensemble neural encoding and to characterize information flow through this system. I will also discuss the major barriers to our progress, and suggest what might be done to overcome some of those barriers. I will focus on problems related to massive data stream analysis and interactive control. In many scientific and engineering disciplines, researchers studying complex systems are being confronted with a fundamental (and seemingly insurmountable) technical problem: how to organize, analyze and understand immense amounts of data, in a manner that allows interaction with the system being studied in real time. For example, neuroscientists studying the operation of the brain would like to record from between 1,000 and 10,000 electrodes simultaneously, at rates of up to 40,000 samples per electrode per second. This represents an aggregate data collection rate of 80 to 800 Megabytes per second. Sensor and data acquisition technology must be advanced significantly to allow this. Even more important, technologies must be developed to allow real-time on-line analysis of such massive data streams, since off-line analysis following data collection precludes the possibility of real-time interactive management and/or control of the system under study. On-line analysis will need to be extremely sophisticated, and provide for extraction and recognition of complex signal features. For example, advanced statistical techniques (including information theory) must be implemented to discover the intrinsic "symbols" within the raw data stream "signals".

Exploiting Neural Tissue: From Algorithms to Animats

William Ditto
Department of Bioengineering
Georgia Institute of Technology

Abstract

Like drinking water from a fire hose we can't swallow much lest digest the torrent of information spewing forth from the confluence of modern biology, computer science and biotechnology. A brief overview of the efforts of both the Neuroengineering Laboratory at Georgia Tech/Emory and Steve Potter's Animat project at Cal Tech will be presented. This will include preliminary algorithms and experiments to manipulate hybrid neural tissue/electronic systems to perform computation. Additionally, results will be presented on the patterns of behavior of animats in virtual worlds controlled by neural tissue.

SESSION 3: Constructing Hybrid Systems

Electrical Cell Signals Measured By Field-Effect Transistors

Andreas Offenhaeusser
MPI for Polymer Research
University of Mainz

Abstract

The combination of biological signal processing elements as membrane proteins, whole cells or even tissue slices with electronic transducers for the detection of physical signals allows the set-up of functional hybrid systems at the borderline between the living and the technical world. This coupling of the high sensitivity and selectivity of biological recognition systems with a man-made signal-detection and processing system will open up exciting possibilities for the development of new biosensors as well as for new approaches in Neuroscience and computer science.

In this paper the basic problems of the coupling of the ionics of individual cells with the electronics of silicon based devices will be addressed. The nature of electrical coupling of the cell with the transistor was determined by means of voltage clamp methods. Combined patch-clamp measurements with transistor recordings showed that the recorded signals are mainly determined by capacitive coupling of the membrane voltage in combination with current signals from functional voltage-gated ion-channels with varying densities in the cell contact area.

Constructing Simple Neuronal Hybrid Devices

James J. Hickman
Department of Bioengineering
Clemson University

Abstract

Biological Computation is an emerging discipline that is primarily concerned with the merging of silicon and biological systems. We are building hybrid devices by directly interfacing cells and microelectronic devices primarily by using self-assembled monolayers (SAMs) to control the intrinsic and geometric properties of surfaces in contact with the biological systems. The use of surface modification techniques allows us to tailor the interface between biological/nonbiological materials independent of the bulk composition of the nonbiological material. Controlling the surface composition of the *in vitro* system as well as other variables, such as growth media and cell preparation, all play important roles in creating a defined system for bioengineering devices. We have used this defined system to culture adult CNS neurons and have demonstrated neuronal process regrowth. We have also shown that the surface composition alone can direct cell fate of embryonic precursor cells during development. We have used the geometric control of the surface composition afforded us by SAMs to create *in vitro* circuits of mammalian neurons. SAMs alone have been shown to differentially effect neuronal adhesion and neurite outgrowth. We have also recorded the electrophysiological signals produced by neurons on the patterned SAMs in response to stimuli. The surfaces have been characterized by X-ray photoelectron spectroscopy (XPS), imaging XPS and contact angle measurements and we have related the intrinsic properties of the surface and the proteins deposited by the cells to cellular development. The continuing development of this technology will be discussed, as well as the implications and applications for (a) biosensor fabrication, (b) neuronal circuit design, and (c) biological computation.

Neurobiological Neural Nonlinear Dynamics for Temporal Pattern Recognition: Biologically Realistic Neural Networks for Signal Processing and Neural Prosthetics

Theodore W. Berger
University of Southern California

Abstract

Dr. Berger will describe a novel neural network architecture based on the nonlinear dynamics of synaptic transmission in the hippocampus, a part of the brain involved in the formation of pattern recognition memories. A combined experimental-theoretical approach based on nonlinear systems theory is used to characterize functional properties of hippocampal neurons and synapses, and in particular, those properties that underlie the sensitivity of hippocampal neural elements to higher-order temporal patterns. These nonlinear transformational characteristics are embedded in neural network models -- "dynamic synapse neural networks" -- and used as the instruments to extract features of temporally coded inputs, e.g., speech signals. A novel "dynamic learning rule," based on adaptive mechanisms of hippocampal synapses, is used to obtain an optimized feature set. Results demonstrate that this approach provides the basis for speaker-independent and speaker-specific word recognition with very small, highly simplified neural networks. Performance of trained networks is highly robust with respect to noise, with systems to date out-performing both human listeners and commercial speech recognition systems. Because the model assumes only neurobiological properties, the system also can be extended to other application domains, e.g., sensor fusion, and represents a new paradigm for identifying fundamental computational properties of the brain. Dynamic synapse neural network models also have been implemented in analog VLSI, and because of their compatibility with real biological systems, are being developed as neural prosthetic devices, for bi-directional communication with the brain. In this regard, novel "neuromorphic" silicon-based multi-site electrode arrays have been fabricated and tested as neuron-silicon interfaces. The spatial distribution of electrode sites is specifically designed to be consistent with the cytoarchitecture of the hippocampus, and brings the uniform distribution of microchip contact pads into the register with the non-uniform distribution of hippocampal neurons.

Using The Posterior Parietal Cortex For A Neural Prosthesis

Richard A. Andersen
Biology Division of Caltech

Abstract

Over the last few years we have identified and studied an area of the posterior parietal cortex in monkeys where the first plans for reaching are formulated. This region also exists in the human brain, and is intact in patients paralyzed due to peripheral neuropathies or spinal cord damage. We are beginning experiments to record neural activity from this area in monkeys using arrays of tiny, implanted electrodes. We hope to "read out" their movement intentions, and use them to operate external devices such as a robot limb or a computer for surfing the internet. If these experiments are successful, than a similar approach may be used in the future to design a neural prosthesis for paralyzed patients.

SPEAKER SESSION NOTES

Friday, January 19, 2001

*It should be noted that each set of session notes was taken by a different graduate student so there are marked differences in styles and presentations.

OPENING REMARKS

Bob Price from DOE introduced the Goal of the workshop to the delegates: seeking guidance and advice for sponsoring areas bordering between Biology and Engineering through active brain-storming between people from varied backgrounds in Biological Sciences, Information Technology, and Engineering.

Rick Adrian from NSF further narrowed down from the above general goal to the aim of NSF: intending to sponsor research in the interface of Biology and Information Technology in a more focused manner.

He explained the importance that NSF understands such an initiative by showing the broad areas of focus identified by NSF for the present and future: Biological Sciences, Computer and Information Science, Education and Human Resources, Engineering, Information Technology, Biocomplexity and Environment and Nanotechnology, etc. He encouraged a rapid response mechanism so that new opportunities can be created within and across the traditional disciplines of science. Such an integrative approach would help us make quicker headway in the areas identified by NSF.

He introduced the following new initiatives of NSF towards a finer interface between Biology and Information Technology:

1) Biomolecular (quantum and DNA computing)
2) Computational Biology (ab initio calculations in biology, drug molecular design)
3) Bioinformatics (data mimics for sequenced homology)
4) Biological Computation (understanding how biology does computing, insilico systems, hybrid systems)

James Hickman from Clemson University and NSF tried to bring home the point of how biology is involved with computing and information processing by giving an example of a cell which does all the functions of an information system: sensor (receptors), data storage (nucleus), information processing (biomolecules), digital and analog out put (ion pumps), customized macromolecular synthesis (golgi apparatus), controlled release (exocytosis), medical signaling (receptors, channels, gates) etc.

So as to have the workshop progress constructively in the correct direction he further defined the working objectives of the workshop, recognizing that this is an interdisciplinary activity and so there would be a number of areas of disagreement:

1) To identify things that everyone agrees on (state of the art areas in biology and information technology).
2) To identify things that everyone disagrees on and identify the reasons (terminology, science, and interpretation). This process would help focus on the areas in which funds should be channelized.

3) To set the short and long-term goals for achieving the defined goals of this workshop and also identifying any hurdles that is likely to be faced in this endeavor.

Ed Uberbacher from Oak Ridge National Laboratory gave the first technical talk, and he tried to highlight the importance of information technology in biology (protein structure predictors) and the way biology process information (cellular information processing and signaling).

Introducing the various types of information, he drew the audience to information in biology: temperature, light, concentration gradient, potential gradient, protein structure, signaling systems, regulatory signals, genes etc. and how this information processing and signaling increased in complexity from single cell organisms through multicellular systems to metazoans. He drew the attention of the delegates to the fact that 50 % of the proteins in a cell were involved in this signaling communication. He then developed this into the bigger picture to show how the biological organisms are complex information processing systems by the way they exercise contingency (a plan for an action that is taken when things go wrong). He gave an example of a simple ad hoc contingency as in the immune response to a virus. He mentioned that the biological systems also show multiple as hoc contingency, and hammered back the fact of multicellular organisms being much more contingent than single-celled organisms. Generalizing on the way most biological systems process information and exercise control, he said that these were mostly steady-state processes.

He mentioned that there were around 16 known mechanisms by which signaling takes place in cells, of which the mechanism using G protein is the only one found in a single cell, while all the other mechanisms of signaling in cells are found in multicellular collections. The G protein signal processing is particularly impressive, in that this protein which is present in the photoreceptors of cells on the retina of the eye, processes a protein in such a way that background noise is kept low.

He then spoke about the correlation between the process of DNA transcription and Boolean algebra. He said that although each and every cell in the body of an organism has the same set of information coded in its genes on the DNA, there is a distribution of genes expressed in different parts of the body. For example, only 20% of the genes are expressed in the visceral organs. So the information is processed in such a way that different types of cells in the body of an organism end up having different sets of genes to work with, although they all have the same genome.

He then introduced the idea of Protein Machines, as complexes of proteins that share the responsibility to do certain functions in processes. He said that every protein binds to some 3000 others, thus displaying a strong potential for forming complexes. But only some of these complexes work as protein machines.

To depict how great a difference computation and information technology can make towards solving biomolecular puzzles, he gave the example of Protein Threading. This is a method of determining protein structure by taking the protein primary sequence and fitting it with other known structures of proteins having a similar sequence, and then modeling the unknown structure in that line by going through an energy optimization process, which is possible thanks to the amazing capacity of the computer to perform complex mathematical operations in a very short time. Threading algorithms complement experimental data, in that we can add constraints in the algorithms, which would be derived from NMR data got experimentally, thereby

increasing the power of this process to figure out unknown structures of new proteins. Mass spectroscopy is also becoming a very powerful technique in providing us with information about what is going on in the cell, especially with respect to proteins. These are the techniques in which research towards obtaining structural information of proteins is rapidly progressing at this point in time.

He then talked about integrating biological process through networks, and suggested 4 types of complementary information pathways to build well-founded biological process networks:

1) Protein Interactions
2) Regulation Networks
3) Signaling Pathways
4) Gene Interactions

He finished his talk by mentioning about "Genomes to Life", a $15million DOE initiative, of which 1/3rd is allocated to computer modeling. This involves for example, microbial cell projects, in which the first thing that is done is to sequence the genome of the microbe. The information that is obtained from this opens up research in a number of fields:

1) Proteomics (protein structure and function)
2) Macromolecular Machines
3) Cell Systems and Networks
4) Microbial Function
5) Biosystem Computer Modeling

Question & Answer Session:

Ruzena Bajcsy: What is the uniqueness in the Threading System for determining protein structure?

The threading algorithm enables development of macromolecular structures, with less experimental information, by doing computational optimization and therefore this system represents a very unique and powerful method in determining the 3D structure of macromolecules.

Ruzena Bajcsy: Why are you talking about a protein machine as an integrator?

The macromolecular signal processing is analog, which is a continuous function. The idea of talking about protein machines as an integrator is in terms of processing information as a continuous function.

Ulrich Egert: How does Mass Spectroscopy (MS) help in giving information about protein complexes other than Molecular Weight determination?

One could spray a cell extract in to the MS and come to know about the MWs of all the proteins in the cell. This is one information that we get. In addition, we can identify which proteins are interacting with which proteins by freezing the reactions using cross linkers and throwing these complexes and their fragments in the MS.

SESSION 1: *In Silico* Systems: From Experiment to Simulation

Laura Landweber from Princeton University, who served as the discussion leader for the first technical session on "In Silico Systems: from Experiment to Simulation" started her introduction but directing everyone's attention to the Universal Genetic Code, a triplet of nitrogen bases that code for the 20 naturally occurring amino acids in all living animals and plants, as a very good example of biological information storage. Raising a very relevant question as to why this code does not change with time, she said that although at the current point of time we do not understand the biological computation processes that occur in organisms on the basis of this code, we can still try to model these processes using computer modeling algorithms and see if we can produce similar results and in that process come up with a mathematical understanding to describe the biological computational processes. Nevertheless, she highlighted the current focus of attention on the genomes of plants, animals and fungi, as being as being just a small step, since there is lots and lots of information storage in the other Eukaryotes, Archaebacteria and Eubacteria, the computational processing of which is currently not under our attention.

Roger Brent from the Institute for Molecular Sciences began his talk on "Information Processing by Cells and Biologists" by mentioning that fields of study like Genetics and Molecular Biology were born from experiments to gain information about coded information. Some of the important questions that have been studied in this regard have been: How is the biological information transmitted from gene to gene? How is it read out into an mRNA? How is this information then expressed? Finally, how is this expression controlled?

On a more generally basis (not considering the information processing and decision making by group of cells like in the nervous system and the immune system), he indicated that cells are like machines that process 3 kinds of information:

1) Information encoded in the genome
2) Information coming from internal events
3) Information coming from outside the cell

According to him biological information processing has been understood to some extent at a certain level which includes protein-protein interactions and protein-DNA interactions, however it has not yet been understood at other levels, so as to get a fully integrated idea of these interactions. Giving an example of a multilevel interaction analysis, he showed a complex circuit diagram which had protein-protein interactions shown as nodes, and the interaction patterns as a whole decide whether a cell will stop following its DNA and lead to cancer or not.

With this background, he posed a question: How are we trying to have a better understanding of processing and decision-making? According to him, an approach of quantitative simulation of biological functions involving continuous and stochastic processes would give predictions as to how the system will behave. However, caution must be taken before accepting the capability of the simulation to truly model the biological system, because simulations are not worth much without supporting experimental evidence. At the same time, the experimental methods that we currently have are completely inadequate to give the kind of information that we need to know to fully understand the biological information processing processes.

The experimental challenges hence forth according to him are in:

1) Single cell measurements
2) Population measurements
3) Strong correlations between experiment and simulations

He summarized his talk with the following points:

1) Information theory has something to contribute to biological information process.
2) Characterizing transmission networks and their components can help in attaining an integrated understanding of biological information processing.
3) We need to identify accurately what the components actually are and then define them with the most appropriate explanatory idea.

Gregory Stephanopoulous started his talk on " A Platform of Flux and Gene Expression Measurements for Metabolic Engineering and Drug Discovery", by mentioning the importance of sequencing of genomes. According to him, this has been the main driver in the development of genomics based technologies like DNA micro-arrays, drug discovery etc. However we need to be able to integrate the information that is becoming available through biology research and there exists great opportunity and scope for quantification of biological information.

We currently have accurate information available from metabolic flux analysis, but still we do not have the complete information to be able to confidently model biological processing systems. With complete information, we will have the ability to make sophisticated inventions like a gene chip that would identify proteins and metabolize them.

From here on he elaborated on Metabolic Engineering and the role played by chemical networks in it. Stating the fact that a bacterium is able to express very specific oxidases and dehydrogenases, which are enzymes that specifically do certain chiral reactions, he said that if we are able to understand this process well then we can engineer biological systems is such a manner that they produce the products of biological interest with a higher yield and under-produce the ones of lesser interest, just like a chemical reactor. Information about the metabolites interacting in a metabolic network can be got using NMR o GC-MS techniques, of which GC-Ms is preferred because of it's low cost and high sensitivity.

He then went on to enlist some computational frontiers that would facilitate understanding in areas linked with metabolic engineering:

1) A quantitative understanding of issues in signal specificity
2) Network based system analysis (Although we know about a number of signaling pathways, we do not know how these pathways communicate/interact with each other.)

He then mentioned some of the frontier areas of research in Metabolic Engineering:

1) Making connections between metabolic phenotype, macroscopic phenotype and expression phenotype.
2) How could this data be obtained so that we can be able to quantitatively understand the physiological state of a cell?
3) Microarray data, which provides good information for drug discovery, towards developing a drug that maximizes the desired effect and minimizes the unwanted side effects.

The following came across, as things that needed to be worked on for the future:

1) Developing new technology for measurement of biological parameters. (The experimental effort necessary to be able to get measurement of the different intermediates in a signaling pathway is really Herculean with the present experimental techniques.)
2) Understanding flow processes, which is a very demanding process in itself.
3) Having an increased acceptance of computed results in the life sciences community.

James Garrels from Proteome, Inc. speaking on "A knowledge resource for the post-genomic era: Turning information buried in the scientific literature into readily accessible knowledge." Gave insight into one of the ways by which information technology can help biology. To give an idea of the rate at which new biological information is being poured in to the scientific world through research every year, he said that there are approximately 3 billion letters (base pairs) in the human genome, 5 billion data points can be got from a DNA chip and 50 billion bytes of new text gets added to the biological literature every year.

According to him a contemporary biology researcher faces the difficult task of integrating data from a variety of different areas, make sense of it and experiment. Some of the areas, which he would have to look in to, would be: the relevant species, the relevant gene involved, the relevant functional genomics (interactions, localizations, post translational modifications, genetic knockouts, expression profiles, co-regulation) and the relevant literature (Genetics, Biochemistry, Developmental Biology, Cell Biology, Clinical Biology, Evolutionary Biology, Structural biology).

To ease this, Proteome Inc. is developing a bioknowledge library with the help of information technology. They have already gathered knowledge of around 20,000 species from some 37,033 papers (curated), which represents decades of published research. Ph.D. s that work with Proteome Inc., as part-time/free-lance curators read and recast the information in the scientific papers, in the form of tables, charts, etc., to have information in a easily managed form. These compiled extracts are then reformatted for access on Internet to increase their accessibility. Each gene that is on this library, would be available on the Internet web page in the following format:

1) Title
2) Properties
3) Annotations
4) References

With the very large rate at which biological information is pouring in (for e.g. approximately 4 new protein complexes are being defined each month.), such databases as the one being developed by Proteome are becoming very big and maturating amazingly fast. Their human database has protein reports available for over 12,000 known human proteins.

Explaining the importance of such an information system, he enlisted the following:

1) Such a system would provide those who are doing science, with a good database providing information from literature in a form, which is easily accessible and easy to work with.
2) Such systems can present extremely complex genetic networks in a very user-friendly manner.
3) Bioknowledge libraries can facilitate tracing of cross species functional connections.
4) Such systems would help in comparing data about known proteins in one organism with a similar less know protein in another organism and trying to characterize the lesser known one.

Question & Answer Session:

Ruzena Bajcsy: How accessible would this service be to the? Would it be free?

The company thinks that such a system should be broadly used. Although there may be certain higher levels related to human data that may be prized at about the rate of a journal subscription, this does not mean that their company would only target business with pharmaceutical companies. Most of the levels of information would be available free on the Internet, for readers.

Ruzena Bajcsy: Are you a unique company?
Up to now, at a large industrial scale, this is a leading endeavor.

How can you make sure that this information is correct?
As one finds contradictory literature in the scientific literature, so it will probably be here too. In the cases where their experts know for sure about the doubtfulness of certain published data, they would add a note of caution.

Ulrich Egert: What are the real IT barriers that one would face to scale up the systems right now to hugely large data? (Like one day there will be an Earth Genome, instead of a human genome.)
The limitation would not come so much from the IT front as it would from the curator front, which will actually read the literature and classify it.

Lila Kari from University of Western Ontario started her quizzical talk with the well-known quotations:
"With poetry and philosophy you can convince those who are already convinced and may be some others, but you can never prove any thing." And
"Science is the only way of shoving ideas down the throats of those who are reluctant."
She thought that DNA knowledge; information theory, theory of computation and the coding theory can together give unified knowledge about biology. Although we do not know the unified theory right now, we should nevertheless imagine that it is present and work towards finding it. She reiterated what Einstein once said, " If we knew what we were doing, it wouldn't be called research, would it?"

Discussion: Information theory seems to match the process of neuron signal transmission but there remain a number of doubts in other areas. So it is inappropriate at this stage to say confidently that information system can model biological information processing.

Ruzena Bajcsy: The unit elementary information is 0 and 1, while the DNA has 4 alphabets. Therefore, it has a much higher level of information. So it would very naïve to say that information theory would work for DNA.

Gregory Stephanopoulous: All biological processes are really observed as a cascade of chemical reactions which have their own kinetics and which are essentially analog in nature and not of a binary on/off type as in digital information theory.

Can any mathematical technique take the information that we know and model the biology?
Gregory Stephanopoulous: Models do not necessarily always predict results that one might find experimentally.
According to Roger Brent, the best mathematical models are those in bacterial chemo-taxis.

Ruzena Bajcsy: If I was a venture capitalist, and I had 4 different options to fund:
1) Development of good analytical instruments
2) Research
3) IT to store research
4) None

What would you advise me to invest my capital in?

Development of good analytical instruments was the answer most people expressed. According to Ulrich Egert, making biologically inspired robots is perceived by many to be most profitable.

EVENING SESSION

Kwabena Boahen from University of Pennsylvania, who functioned as the moderator of the session after dinner, gave some interesting comparisons between biological processing speed and electronic/computer processing speed. 10^{16} synaptic events occur per second inside the human body using about 10 watts of power, while 1 petaflop (a hi-tech microprocessor which IBM will be introducing) will be able to do only 10^{15} instructions per second using 10^{6} Watts. While the transit time for charges (ions) in an ion channel is 10^{-8}s and the switching energy involved is 10^{-18} J, the transit time for charges (electrons) in a transistor is 10^{-12}s and the switching energy involved is 10^{-15} J. There are around $1*10^{10}$ neurons, $6*10^{13}$ synapses, $4*10^{15}$ bits in brain and $3*10^{9}$ bits in DNA. Thus indicating the areas where biology processes information more efficiently than the electronic microprocessor, he introduced the idea of morphing brain circuits into silicon chips, towards developing advanced processors.

Frederica Darema from NSF speaking on "Synergistic Approaches for Creating Neurobiologically Inspired Computing Systems", said that NSF wishes to promote new computational paradigms: to design and build machines (computers, robots, prosthetic devices) that process information with human like intelligence and Von Neumann system capacity. (Von Neumann systems can do complex numerical calculations at speeds not matched by humans, with silicon based technology while biological systems can do the functions of sensation, vision, motion, inference and association much better than a Von Neumann system, using neuronal technology.

With the above comparison, she laid down one of the objectives, which NSF intends to promote: To determine and define what neurobiology can do for computer science, not what computer science can do for biology.

To be able to achieve the above objective, we need to answer some questions:

1) What tools are needed to understand physiological processing of information?
2) How to emulate the physiological information processing? What kind of computer systems (architecture, organization) can be derived from them?
3) Are there any new representations for information processing?
4) What underlying technologies are needed to design and build such systems?
5) Is focus on just device designs sufficient for attaining the ultimate objective?

According to her, the above objective should be clearly distinguished from computational biology applications, genome mapping and biological databases. What is more appropriate realistically is the need for better modeling methods for advancing the understanding of biological systems. Such understanding requires multi-level and multi-mode modeling methods; biological system level modeling rather than just component level modeling. Better understanding of the fundamentals would make things easy in this endeavor.

She mentioned about a series of Government agency efforts in this direction, like the May 1996 NSF workshop on multidisciplinary research scope for biologists, engineers, computer scientists, mathematicians and physicists and the DARPA ultra computing project.

In this line, we need to have some programmatic considerations:

1) We require chalking out a program with long-term objectives.
2) We need to examine what can be some of the 5, 10, 20 years milestones.
3) Such research will have to be multidisciplinary collaborative endeavors.
4) Is the community ready for this?

One good approach towards approaching such types of projects would be to have dynamic data driven applications systems, which would involve a feedback control loop between the first principles from theory, the mathematical modeling and simulations and the experimental data.

She said that applications software development would be one of the challenges that we would have to face.

Gary Strong from NSF, spoke on "Information: the Language of Biology". He said that both natural language and biology are faced with data mining. Data mining for protein and biological function through regulatory pathway research is growing exponentially generating huge amounts of information. I we can develop a grammar that explains the language of biology, then we will be able to predict the structure and function of biology. He suggested new approaches for gene identification, structure prediction and circuit discovery (protein interactions, signal transduction).

Giving an example of how this can be done, he talked about the components of a successful program for natural languages at DARPA:

1) Data needs to be shared across the research community, which implies enforcement of certain annotation standards.
2) Objective community wide evaluations.
3) Technology transfer must be faster.
4) National challenge problems do exist and can unify federal support.

He also referred to successful human language programs at IBM, AT&T and Lucent Technologies.

Introducing a concept of remote sensing for biosurveillance, he posed two questions:

1) Can we model the progress of a disease as a sequence of break points?
2) Can we forecast the spread of a disease as we forecast weather?

His concluding remarks were;

1) There are strong parallels between natural language and biological data, affording the development and use of common tools.
2) DARPA style program elements may be appropriate for bioinformatics.

Discussion:

What is the information unit in the brain?

We do not have a theory of computation for the brain and therefore we do not have a definition for an information unit processed in the brain.

The information is coded and the way neural connections are made determines the power that is required for the information processing.

Hickman: Language has a structure/syntax. Similarly, cellular processing have syntax. Are there any correlations between these and natural language?
No proper answer was got for this question. There are tools developed for data mining in natural language.

Saturday, January 20, 2001

"Brains On Chips: Neurobiology From Basic to Applied Science" Ulrich Egert (Albert-Ludwig University)

Neurons in and of themselves are not static units. They function in complex networks. The speaker has designed novel microelectrode arrays (MEAs) that are capable of recording information from intact neural networks. The microarrays consist of grids between 100-200 □m with electrodes of 10-30 □m in diameter. The speaker has used these arrays to analyze local field potentials and perform neuronal plasticity studies in rat hippocampal cells. By electrically stimulating slices of PN day 15 rat brain on the electrode arrays, it is possible record the responses of the surrounding neurons. Color coded graphs of electrical activity show the voltage distributions corresponding with anatomical features. These graphs can then be animated to show real time progression of the voltage front.

Possible applications of this technology include use as an assay for dopaminergic drug development. Proteins targeted by dopaminergic drugs are relevant targets for treatment of Parkinson's disease and schizophrenia. This technology would offer a faster method for determining how an experimental drug affects the neural pathways. However, this assay will not show what a drug is actually doing; only the pathways it is affecting. Other applications are also proposed such as, retina research, neuronal prostheses, cardio pharmacology, and long-term recording of circadian rhythms

New technological developments will extend the range of functions and applications of these arrays. 3D electrodes with protruding pins have been developed for recording in deep tissues. These may penetrate up to 2 mm and record for extended periods of time. The next step will be to design custom MEAs for complex tissue geometries. MEAs will prove very useful in designing efficient functional *in vitro* assays, long-term monitoring of functional development and regeneration, and developing the concepts for the control of prosthetic devices.

SESSION 2: Multi-Cellular Information Processing

"Neuromorphic Information Processing" Jacob Barhen (Oak Ridge National Laboratory).

This session deals with how to apply computational devices that mimic neuronal behavior. Neuromorphs promise to ultimately help in the processing of highly complex information. These systems are adaptive systems that process information by means of their response to discrete or continuous data. However, little is known about the coding schemes of neural systems. How many coding schemes are there? What is the coding system for sensory, motor, cortical pathways, etc? What are the dynamics of these systems? And, most importantly, how to decode these systems? Other challenges lie in mimicking how neural systems learn and adapt. The speaker proposes that five to ten years from now technology that integrates physics and biology will revolutionized computational science giving researchers unprecedented computational power enabling novel processing paradigms.

"Information Processing in Cortical Circuits: Temporal Multiplexing and the Search for the Canonical Microcircuit" Todd Troyer (University of Maryland).

Given the inherent complexity of information processing on cortical networks, it is necessary to rely on simplifications and focus on underlying principles in order to understand them. One such simplification is the assumption that neurons use some sort of "rate code." Although subject to

intense scrutiny, this assumption has held up well experimentally. However, most likely these systems use multiple coding schemes, which are multiplexed in time, thereby making decoding an extremely difficult task.
Improvements in patch clamp recording techniques, both *in vitro* and *in vivo*, as well as increased use of multi-electrode recordings are generating a wealth of data. However, while theoretical progress is being made, general principles await discovery. The speaker discussed several models for understanding the neural code, but focused on identifying problems to be solved and possible applications of these principles.

"Biological Neurons, Electronic Neurons, Neural Information Processing" Henry D. I. Abarbanel (Scripps Institute of Oceanography).

The speaker's interest's lie in studying neural networks made from marine invertebrates and electronic neurons (ENs). The ENs are designed to reflect the four degrees of freedom found in the bursting pattern of neurons taken from central pattern generator neurons of the California spiny lobster. The ENs quantitatively reproduce the firing patterns of isolated biological neurons and show strikingly realistic interactions with each other and biological neurons. By replacing neurons in biological circuits, ENs have been shown to interact with each other in small networks just as biological neurons do.
The speaker has used "channels" of ENs, coupled with analog circuit synapses and computer synapses (dynamic clamp) to explore information transport in neuronal circuits. How and where the information is coded and decoded are key issues. ENs have shown themselves to be very useful to this end thus far and a conceptual step in the right direction. The other attendees commended this work and discussed its potential at length.

"Analysis of Neural Encoding In Sensory Systems: Progress and Barriers" John Miller (Montana State University)

There are many basic challenges and questions to be answered in figuring out how the brain works. So, what qualifies as an adequate level of understanding? We need to have a good knowledge of the tasks being performed, the algorithms being implemented, the computational architecture of the network, and the detailed circuit and its relevant functional components. Answering these questions will require the development and application of new analytical approaches, new tools for the acquisition and analysis of massive data streams.

The speaker's strategy has been to use analytical approaches from information theory to study ensemble neural coding and characterize information flow in a simple sensory system. Readings are taken from intact sensory circuits of live crickets. The action potentials are then recorded over different neurons, allowing researchers to study the distribution of action potentials. Results from such experiments have been used to answer questions of how the code is broken up over different pathways. Distributed codes over ensembles of cells is a difficult problem and may be impossible to decode or recreate with current tools.
The largest current technological barriers to these efforts are due to the massive data streams analysis and interaction control. Large amounts of data must be recorded, stored, and analyzed for thousands of neurons. However, with current technology it is impossible to acquire and analyze this data in real time. Without this ability we cannot decipher the symbols from the raw signals and decode the information. We are able to acquire data from biological systems, discriminate the data, and decode it experimentally. However, this cannot be done "on-line" and interactively.

New technologies must be developed to enable long-term simultaneous recording of activity patterns. These technologies must record massive amounts of data with very high temporal resolution. Also, these technologies must allow for "on-line" data processing allowing for experimental manipulation of closed-loop laboratory preparations, again over long periods of time. Otherwise, we are constrained to store the data and analyze it "off-line".

"Exploiting Neural Tissue: From Algorithm to Animats" William Ditto (Georgia Tech).

The speaker has developed a "Doom-like" computer game, which is run by rat cortical cells cultured onto microelectrode arrays (MEAs). These devices are being used to investigate the use of cultured neural tissue for computing purposes. The program consists of an Animat in a virtual environment, which is controlled by the neural cells. The speaker showed a demonstration of the Animat moving through and avoiding obstacles in the virtual environment. Potential benefits of such systems include increased processing speed and energy efficiency.
These preparations are promising, and have been shown to live for over one year on the MEAs. Also, these preparations are rigorous systems where inputs and outputs can be controlled. Experiments in further manipulating hybrid neural tissue/electronic systems to perform computation.

"Functional Interfaces with Retinal Neurons" John R. Hetling (University of Illinois at Chicago)*.

The speaker's work focuses on the development of retinal prostheses. Current issues included discussion regarding optimal locations for implanting such prostheses. Several proposed areas include implantation at the photoreceptors, RPE, conjunctiva, and epithelia. Other issues include questions regarding the types of information that needs to be relayed in order to make functional prostheses. The speaker's future work will address these matters.
***5-minute presentation.**

SESSION 3: Constructing Hybrid Systems

Bruce Wheeler, Moderator
Cochlear implant is the most successful example of a biohybrid.
Questions:
What are useful biological computing elements? Biosensor or reporter, prosthetic input/output sensory or motor?
Can we construct neural system? Synthesis of neural net in dish.
What tools to we need for further work?
What modeling advances needed? Data compression, novel correlation features.
What neural organization levels are effective? Subcellular, tissues.
Constructing Hybrid Systems: Tools, Models, Design, Engineering Concerns.

Andreas Offenhaeusser, "Electrical Cell Signals Measured by Field-effect Transistors"
Two motivations:

- use cells as sensor elements and record chemicals which interact and change electrical properties
- neuronal networks as elements for bio electronic signal

Talk in 3 parts: detection system, cell detector coupling, guided cell growth.

1) Measurement system: field effect transistors (FET), place cell on top of gate and record change in current, or use metal microelectrode connected to FET outside of dish
FET translates change at gate potential in current source to drain, change of gate potential forms channel and is modulated
4x4 matrix FET with common source and individual gate, mount FET on chip and form culture dish
Second device uses metal electrodes 8x8, not limited to metal, for example silicon-silicon oxide, submicrometer. Encapsulated on chip carrier, forms culture dish. Advantage of this is can change dimensions plateaus, tips.

2) Cell detector coupling
How is cell signal translated into signal from detector?
Cardiac myocytes cultured on FET; signals completely different, correlated in time but different shape, how to explain?
Affects FET and gate effect same way, true for both.
Point contact model, assume extracellular potential is one point, not distributed area, need two components to explain signals, capacitance of membrane and ionic current going through ion channels in membrane in contact with gate.
If no ionic current present, easier to see
If ionic current, assume current enhance at least by factor of 2.
Control voltage of cell with patch pipette and measure signal by FET.
Coupling recordings show two components in both sodium and potassium currents.
Can block potassium channel with TEA (triethylamine), confirms.

3) Guided cell growth.
Use microcontact printing from master stamp.
Use brain slices just as supply of healthy neurons, cut and place next to pattern, cells grow out of slice and are guided by patterning if you use only small thin lined, you get only axons, with wider lines you get cell bodies, mixture of glia and neurons.
Cannot identify which neuron is connected with which, use microstaining with fluorescent dye which diffuses, can establish connections.
Patch clamp technique to study how signals transmitted and can study 3 neurons at once.
Three coupling types: 1) ohmic coupling, leak resistance; 2) capacitive coupling, transfer capacitance; and 3) functional coupling.
Lastly, bring patterning together with recording device, align microstamp and chip and transfer pattern onto device.
Test with other cell line which overgrew substrate, will use neurons next.

Q: When saw capacitive coupling, how much voltage induced?
A: A few percent, very low.

Q: Have you tried techniques to bias capacitance? Coupling between cells?
A: Yes tried, not succeeded yet, not sure why, only 5% functional couplings.

Q: Most cells stay on line for day then move off, how long do your cells stay, how useful is microstamp if cells don't stay?

A: Depends on surface chemistry. If you can have high contrast between cell attractive and repulsive, our patterns are stable for at least 3 weeks, some tensions exist, but 90% look the same after 3 weeks.

Q: But in other work, only stayed when had nodes for cells to rest.
A: Yes, it takes four to five days to stabilize.

Q: Opportunity because of different signal between micropipette and FET, testing of drugs with micropipette not giving answers, could investigate this?
A: We have investigated this. It is possible to do this and we have seen results.

J. Hickman, "Constructing Simple Hybrid Neuronal Devices"

Walk through idea of trying to make hybrid systems part silicon part neuron.
To engineer system like this, looking at cells as sensor elements, need filters, valves, etc. Need to have specifications so others can build it. Biology has basic systems, want to make it complicated.
Variables: surface growing on, SAMS, proteins, peptides, geometric patterns; media need to approximate cerebrospinal fluid, no serum, makes it simpler to not have proteins, only deposition comes from cells; cell age, limited to embryonic cause others won't grow, recently adult cells have been successful; cell preparation, mechanical vs. enzymatic these produce entirely different effects; different cell types, neurons, astrocytes, oligodendrocytes, microglia.
Cartoon of system neuron on proteins on surface layer on bulk material, relationship with media.
SAMS simple process to prepare monolayer with unique functional (R) group which you can use as is or attach proteins to; surface analysis yields good info.
Picture of neurons on deposited SiO_2, can see healthy neurons, even stain well for doubters.
Cortical cells from adult rat illustrates tools, parameters of system proved.
Want to transduce signals, are working on surface chemistry to get one to one correspondence.
Signals obtained from spinal neurons, myocytes have better signal to noise as opposed to spinal which relies on cell being in right spot.
Trying to get more info out of single cell, can have independent measurements if get them all on electrodes.
Signals must affect action potential, many compounds do this, can do real time analysis of system can collect a lot of data very quickly.
Want to control cells connection, use surface chemistry to create pattern, SAMS with amines and backfill to create circuits, can get in 50% success rate of fidelity.
Neuron has polarity, can use surface chemistry to control this too by using smart patterns, 92% of time can control dominant process.
Dual patch clamp recording in simple two cell circuit, stimulate with one and record with other to see if synapse connection.
Patch clamp technique won Nobel Prize, simple technology.
Pattern evoked signals after 12 days; shows can add things to stop more synapses, again gives more control.
How to get info? Create system you know something about and tweak it. Simulation of simple circuit of inhibitory and active neurons.
Main factors for central nervous system: good control of surfaces, media, can use adult or embryo, good cell preparation and cell types. We have all the tools necessary to build simple systems and detailed parameters that others can use as well.

Allows us to go back to original diagram and start building systems using other cells, like muscle for gate or liver for filtration etc., no longer care what is biological or not.

Q: Did you grow neurons on germanium?
A: No, haha.

Q: What will you do with chips with patterns?
A: Use to understand how info is being processed in neuronal system.

Q: Any target gizmos you want to build?
A: Just want to reproduce circuits I am familiar with, whether they will work the same way.

Q: What are uses?
A: Sensors.

Q: What improvement on functional genomics?
A: Bottleneck is high throughput electrophysiology, this methodology allows collection of temporal information that is much cheaper than the way they're doing now, much more efficient, all surface chemistry and lithography, this will be first germane application.

Q: Role of glia in this, can you control?
A: Haven't tried yet, whole lot of basic info to get out of simple systems now, then add.

Q: All hybrid systems couple electrical device and cell capable of evoking action potential. There are other hybrid systems with other cells that will be useful, for example information theory of signal transduction, non-electrical cells?
A: George Whitesides working on this.

Q: Writing piece of DNA in response to electrical signal, possible with all cells?
A: All cells have membrane potential, white blood cells.

Q: But slow, cannot measure slow changes?
A: Can look at using patch clamp, if need can develop systems.
A: Could measure impedance changes.

Q: Germanium transistor 28 years ago, where are we going in next few years?
A: Four companies selling solid state systems, lots of funding from drug discovery, gone from first experiment to commercialization.

Q: But what is capability of systems, compare to PC and transistor?
A: Predict in next five years real growth; put a lot of money into PC project, has been a lot less investment in this and as a result growth has been slower but it is worthy of investment.

Q: Real question is whether you can control and build situation where you can get predictable results, where is the theory?

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Clemson University, January 19-20, 2001

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Speaker Biographical Sketches

Dr. Robert Price, Director from DOE in the Basic Energy Engineering Sciences.

Dr. Rick Adrion rejoined CISE after a 14-year absence in January 2000. He is Professor of Computer Science at the University of Massachusetts, Amherst and Director of the Center for Research on Intelligent Complex Computing Systems. He served as chair of the department from 1986-1994. **Adrion** founded and served as president and chair of the board of the Applied Computing Systems Institute of Massachusetts--a corporation designed to transfer technology developed at the University of Massachusetts. In addition to UMass and previous service at NSF, he has held permanent and visiting positions with the University of Texas, Austin, Oregon State University, National Bureau of Standards, American University, Georgetown University, the University of California, Berkeley and the Université de Paris-Sud Laboratoire de Recherche en Informatique. **Adrion** was the founder and served as Editor in Chief of ACM Transactions on Software Engineering and Methodology and is a fellow of the ACM and of the AAAS.

Dr. James J. Hickman is the Hunter Endowed Chair in the Bioengineering Department at Clemson University. He is also serving part-time as a special advisor to the Director of EIA/CSE/NSF for biocomputation. He obtained B.S. in 1983 at the Pennsylvania State University, M.S., 1985 at the Pennsylvania State University and Ph.D., 1990 at Massachusetts Institute of Technology. He ran a bioelectronics facility from 1990-97 when he moved to academia in the Chemistry Department at the George Washington University. He is interested in interface and surface chemistry, bioelectronics, sensors, biocompatibility neuroscience, genomics, and drug discovery. Previous projects focused on using surface chemical modification and analysis for applications such as engineering biocompatibility for CNS implants, *in vitro* cell patterning, studying cell-surface interactions both *in vitro* and *in vivo*, the development of cell-based biosensors and novel neuroelectric hybrid devices, biocompatible MEMs, as well as function-based assays for drug discovery. Current areas of research in Dr. Hickman's lab include: function-based biosensors for use in toxins detection, fabrication of novel neuroelectric computational devices, cell-based assays for gene function analysis, development of an *in vitro* model of the reflex arc for rehabilitation**,** surface modification for biocompatibility, and biocompatible MEMs.

Dr. Edward C. Uberbacher received his B.A. degree from the Johns Hopkins University in 1974, and PhD in chemistry from the University of Pennsylvania in 1979, with a thesis in the area of macromolecular crystallography. Starting in 1980, he did post-doctoral studies at the University of Pennsylvania Department of Biophysics (Johnson Foundation), and the Biology Division of Oak Ridge National Laboratory - University of Tennessee Graduate School of Biomedical Sciences, investigating the structure and function of genetic materials using crystallography and tomographic image reconstruction in the electron microscope. In 1985 he became a consultant at the Center for Small-Angle Scattering Research at ORNL, pursuing structural and dynamic studies of macromolecules in solution using neutron and X-ray scattering techniques. In 1987, he also became a Research Assistant Professor at the University of Tennessee Graduate School of Biomedical Sciences, and an investigator in the ORNL Biology Division, focusing on X-ray and neutron crystallography and scattering, and other biophysical methods. In 1988 he became a consultant at the ORNL Engineering Physics and Mathematics Division to develop AI and high-performance computing methods for genomic DNA sequence analysis, and in 1991 joined the staff of the Computer Science and Mathematics Division as the

Informatics Group leader where he received an R&D 100 award for the development of the GRAIL DNA sequence analysis system. In 1997, he became the head of the Computational Biology Section in Life Sciences Division ORNL and is also currently an adjunct Associate Professor in the Graduate School of Biomedical Sciences at the University of Tennessee (Knoxville). His interests include the application of pattern recognition, artificial intelligence, and concurrent processing techniques to computational biology, genome analysis, and macromolecular structure and dynamics.

Dr. Laura Landweber graduated from Princeton in Molecular Biology in 1989 and received her Ph.D. from Harvard University in 1993. She was a Junior Fellow of the Harvard Society of Fellows for a year and then returned to Princeton, where she has been an Assistant Professor of Biology in the Department of Ecology & Evolutionary Biology since 1994. She is a member of the science board and has been a fellow-at-large of the Santa Fe Institute and has received Burroughs-Wellcome Fund and Sigma Xi New Investigator Awards for her research which spans the interplay between molecular biology, computer science, chemistry, and evolution. Her main interest is the evolution of genetic information processing, both in test-tube experiments in the laboratory and in organisms as far ranging as ciliates or trypanosomes (the agents of African sleeping sickness). Her work on "gene unscrambling" and "RNA editing" in these organisms offers a fresh way of thinking about how to construct genes from cryptic pieces of the genome as biological computation. Other work in her laboratory has shed light on our understanding of the origin and evolution of the Genetic Code. The most recent focus of her lab has been the construction of RNA and DNA "computers" that solve mathematical problems with evolution. Together, these approaches explore the origin, function, and *potential uses* of biological information. In the past few years, Laura has organized four conferences at Princeton, including two which celebrated Princeton's 250th anniversary and an international workshop on "Evolution as Computation" that helped launch this new field.

Dr. Roger Brent was born in Spartanburg, South Carolina in 1955. He graduated from the University of Southern Mississippi with a BA in Computer Science and Mathematics in 1973, where he did some work attempting to apply AI techniques to protein folding. He received a Ph.D. from Harvard University in 1982 in Biochemistry and Molecular Biology for studies with Mark Ptashne. As a graduate student, he showed that the *E. coli lexA* gene repressed genes involved in the response to radiation damage, cloned the gene, produced and purified its protein product using and in some cases extending the newly developed recombinant DNA methods, and studied binding of the repressor to its operators, showing that its differential binding affinity for these sites affected the timing of the response. As a postdoc, also with Mark Ptashne, in order to test a number of ideas about the mechanism of transcription regulation in yeast, he used the prokaryotic LexA protein and then chimeric proteins that carried LexA fused to activators native to yeast. These "domain swap" experiments established the modular nature of eukaryotic transcription regulation. As a professor at MGH/ Harvard Med (Genetics, starting 1985), Brent and coworkers used yeast transcription that depended on chimeric DNA bound proteins as a genetic probe for protein function in higher organisms. This work led to the development of working two hybrid methods (1988-1993), to the ability to scale them up via interaction mating (1992-1994), and to the parley of protein interaction as a broad but shallow way to learn more about biological function. In parallel (1993-2000), Brent and coworkers have developed peptide aptamers as reverse "genetic" agents to study the function of proteins and allelic protein variants, and, more recently, as dominant "forward" genetic reagents to identify genes and pathway linkages in organisms, such as human cells, that are intractable to classical genetic analysis. Perhaps as important as the actual technologies is the parallel development by Brent and

coworkers of ideology (e.g. doctrine) for using them. Development of this work is chronicled in about 70 research papers and reviews. In parallel to this academic work, Brent is a longtime (since 1984) advisor to the biotech, and the pharma industry. He sits on the SAB of American Home Products (GI/WAR), chairs a think tank for a startup company called CIStem, and does a great deal of ad hoc consulting work in the areas of genomics and computational biology. He is one of the founders (since 1987) of Current Protocols, including Current Protocols in Molecular Biology, the single best "how to clone it" manual, which is updated every three months and has about 10,000 subscribing labs, and he is founder and organizer (since 1994) of the "After The Genome" workshops. He is an inventor on 9 issued, 1 allowed, and 1 pending US Patents. Since the middle 1990s, he has exhorted and advised various bodies in the US and abroad on functional genomics and computational biology, and has worked with the DARPA and other parts of the US Defense Department. In 1998, Brent started, with Sydney Brenner, The Molecular Sciences Institute. TMSI is a start-up, non-profit, research institute in Berkeley, California (www.molsci.org). The MSI mission is to create a predictive biology by weaving together functional genomic and other experimental information and using it to make predictive simulations of biological function. If successful, work at the Institute will also hasten the rise of a design based engineering of biological systems. In 2000, Brent joined the faculty at UCSF as an adjunct professor, if the MSI survives, it will move to UCSF or to another research university.

Dr. Gregory Stephanopoulos is a Professor of Chemical Engineering at MIT. He received his B.S. Degree from the National Technical University of Athens, M.S. Degree from the University of Florida and his Ph.D. Degree form the University of Minnesota, all in Chemical Engineering. He joined, upon graduation in 1978, the Chemical Engineering Faculty of the California Institute of Technology, where he served as Assistant and Associate Professor until 1985. In 1985 he was appointed Professor of Chemical Engineering at MIT where he has been ever since. Professor Stephanopoulos' research interests span a broad spectrum of biotechnological applications. His current research focuses on the *cultivation and physiology of mammalian cells* (in particular, investigation of cell death in sustained cell culture, glycosylation and regulated secretion), *metabolic engineering* and its applications to the production of amino acids and biochemicals, and *bioinformatics and functional genomics* whereby new genomics-based technologies are applied to the elucidation of cell physiology and metabolic engineering. Professor Stephanopoulos' work has appeared in more than 185 publications and 7 patents. He is presently serving on the Editorial Boards of 7 scientific journals and he is the co-editor-in-chief of the journal *Metabolic Engineering*. He has been recognized with the Dreyfus Foundation Teacher Scholar Award (1982), Excellence in Teaching Award (1984) and Technical Achievement Award of the AIChE (1984). He has been a Presidential Young Investigator and the Chairman of the Food Pharmaceutical & Bioengineering Division of the American Institute of Chemical Engineers (1992). In 1992 he was a Visiting Professor at the International Research Center for Biotechnology at Osaka University and was elected a Founding Fellow of the American Institute for Medical and Biological Engineering. In 1996 he chaired the first Conference on Metabolic Engineering and gave the inaugural Bayer Lecture on Biochemical Engineering at the University of California at Berkeley. He was honored with the FPBE Division Award at AIChE in 1997. Professor Stephanopoulos has taught a variety of undergraduate and graduate courses in the Chemical Engineering curriculum at Caltech and MIT. He has also developed a number of new classes including *Metabolic Engineering*, *Metabolic and Cell Engineering* and, more recently, *Bioinformatics.* He has co-authored the first textbook on the subject of Metabolic Engineering and participated in the teaching of a number of biotechnology courses in the MIT summer sessions since 1985. He introduced and co-directed two such courses on the subjects of Metabolic Engineering and Bioinformatics.

Dr. James I. Garrels is President and CEO of Proteome, Inc. based in Beverly, MA. Dr. Garrels and Dr. Joan E. Brooks founded Proteome, Inc. in 1995, realizing the opportunity that was opening to combine protein information with the coming explosion of genomics data. Proteome is a knowledge-based company that has created the BioKnowledge Library, a resource of protein information extracted from the biological literature by expert curators and integrated with genomics and proteomics data as a tool for discovery. Dr. Garrels was previously Director of the QUEST Protein Database Center and Senior Scientist at the Cold Spring Harbor Laboratory. At Cold Spring Harbor, he was an early developer of two-dimensional gel technology and databases, and he has published many articles on analysis of the proteomes of mammalian and yeast cells. Dr. Garrels began his work in proteomics at the Salk Institute and at the University of California, San Diego where he received his Ph.D. in 1978. Prior to that, Dr. Garrels studied at Caltech where he received a B.S. in physics and biology in 1971.

Dr. Kwabena Boahen's current research interests focus on (1) understanding neurobiology by synthesizing integrated electronic circuits with similar functions and related structural correlates, and (2) developing large-scale models of cortical processing using mixed analog/digital multichip architectures & asynchronous communication. Dr. Boahen is one of the young leaders of the field of neuromorphic engineering. He is a neurobiologist who is using integrated circuits to understand the way neurons compute, linking the seemingly far apart fields of integrated circuits and computer science with neurobiology

Dr. Frederica Darema is the Senior Science and Technology Advisor at EIA and CISE, and Director of the Next Generation Software Program. Dr. Darema's interests and technical contributions span the development of parallel applications, parallel algorithms, programming models, environments, and performance methods and tools for the design of applications and of software for parallel and distributed systems. Dr. Darema received her BS degree from the School of Physics and Mathematics of the University of Athens - Greece, and MS and Ph. D. degrees in Theoretical Nuclear Physics from the Illinois Institute of Technology and the University of California at Davis respectively. After Physics Research Associate positions at the University of Pittsburgh and Brookhaven National Lab, she became a Technical Staff Member in the Nuclear Sciences Department at Schlumberger-Doll Research. Subsequently, in 1982, she joined the IBM T. J. Watson Research Center as a Research Staff Member in the Computer Sciences Department and later-on she established and became the manager of a research group at IBM Research on parallel applications. While at IBM she also served in the IBM Corporate Strategy Group examining and helping set corporate-wide strategies. In 1984 Dr. Darema proposed the SPMD (Single-Program-Multiple-Data) computational model which has become the popular model for programming today's parallel and distributed computers. Dr. Darema has been at NSF since 1994, where she has developed initiatives for new software capabilities, a new paradigm for applications, and pushing for research in the interface of neurobiology and computing. During 1996-1998 she completed a two-year assignment at DARPA where she initiated a new thrust for research on methods and technology for performance engineered systems.

Dr. Gary W. Strong is a Program Manager for the Communicator and TIDES Programs, ITO. Prior to Dr. Strong's assignment at DARPA, he was Program Director, Human Computer Interaction Program, for the National Science Foundation (NSF). He has also served as Program Director, Interactive Systems with NSF. Since 1982, Dr. Strong has been a Tenured Associate Professor, Drexel University, College of Information Studies.

Dr. Ulrich Egert received his Vor-Diplom (B.S. degree) in 1982 from the University of Tuebingen. He attended graduate school at Duke University and the University of Tuebingen. He received his Ph.D. degree in 1995. and now serves as the Head of the applied science lab in the Neurobiology and Biophysics Department at the Albert-Ludwigs Univ. Freiburg. The main research topics in his lab are (1) to design, implement and test tools that allow the assessment of a test-drugs effects on neural networks in vitro, (2) to capture and understand the spatiotemporal dynamics of neuronal activity in brain slices, and (3) to develop tools that allow us to visualize and interpret the spatial distribution and the temporal structure of the activity detected.

Dr. Jacob Barhen is the Director of the DOE-established Center for Engineering Science Advanced Research (CESAR) at the Oak Ridge National Laboratory (ORNL). Concurrently, he also serves as Manager for CESAR programs within ORNL's Computing and Computational Science Directorate, and Manager of the Engineering Science Program within the Physical and Chemical Sciences Directorate. In March 1999, he was named *Corporate Fellow* of the Lockheed Martin (LMER) Corporation. In August 2000, he joined the Battelle Technology Council. He is also a non-resident affiliate of the California Institute of Technology's Jet Propulsion Laboratory (JPL). From 1987 to 1994, Dr. Barhen was the head of the Nonlinear Science and Information Processing Group at Caltech / JPL. He began his career at ORNL, where he headed the Machine Intelligence Group from 1978 to 1987. At both institutions, he established world-class research groups in artificial neural information processing and computational science. He has been the principal investigator of numerous basic and applied research projects funded by U.S. Government agencies. Currently, the DOE Office of Science, NASA, the Missile Defense Agency, and the National Reconnaissance Office support his work. Additional information can be found at URL: www.cesar.ornl.gov. Dr. Barhen's research interests include (*i*) global optimization; (*ii*) neural networks; *(iii*) emerging computational systems; and (*iv*) optical information processing. He has authored over 160 scientific papers, and holds 8 U.S. Patents. During his tenure at Caltech/JPL, he was nominated to the U.S. Air Force Science Advisory Board. Dr. Barhen received his D.Sc. degree from the Technion-Israel Institute of Technology, Haifa, in 1978. He is a member of the AAAS, IEEE, SPIE, the International Neural Networks Society, and the Planetary Society. He holds an active DOD/DISCO clearance.

Dr. Todd Troyer is an Assistant Professor in the Department of Psychology at the University of Maryland, College Park. He received his B.A. (Math/Physics) from Washington University in St. Louis in 1985. He received a Ph.D. (Math) from the University of California, Berkeley in 1993 and has had postdoctoral training (Computational Neuroscience) at the University of California, San Francisco. His research interests include: Applying computational techniques to understand the neural mechanisms subserving complex temporal behaviors. Specific projects include fine-grained analyses of avian vocalizations recorded from developing birds, and the nature of neural encoding and dynamical processing in models of neurons and neural circuits.

Dr. Henry Don Isaac Abarbanel is a Professor of Physics in the Marine Physical Laboratory, Scripps Institution of Oceanography and the Department of Physics at the University of California, San Diego. He received his B. S. Degree in Physics from the California Institute of Technology in 1963 and his Ph.D. in Physics from Princeton University in 1966. Dr. Abarbanel is a member of UCSD Neurosciences Graduate Program. He has served as Chairman of Special Interest Group for Dynamical Systems, Society of Industrial and Applied Mathematics, Chair, University of California – NASA, Steering Committee for Joint Program in Nonlinear Science,

Chairman, California Coordinating Committee for Nonlinear Studies of the University of California, and is presently the Director, Institute for Nonlinear Science at the University of California, San Diego and is a Research Physicist at the Marine Physical Laboratory. Dr. Abarbanel is currently serving as Editor-in-Chief, Springer-Verlag Series in Nonlinear Science, and was a member Office of Naval Research Board of Visitors in Physics.

John P. Miller, Ph.D. is a professor of Cell Biology and Neuroscience, and Director of the Center for Computational Biology, Montana State University, Bozeman. Dr. Miller's research focuses on the biological mechanisms underlying information processing in nervous systems. Dr. Miller uses a combination of experimental and theoretical analyses in his work. His recent research has focused on the applications of information theory to the analysis of neural ensemble activity patterns in the cricket cercal sensory system. Dr. Miller received his B.A. in Physics at the University of California, Berkeley, and received his Ph.D. in Biology at the University of California, San Diego, 1980. After completing his thesis research, Dr. Miller did postdoctoral research in the Math Research Branch at the National Institutes of Health in Bethesda, MD. His co-sponsors were Dr. Wilfrid Rall and Dr. John Rinzel. Dr. Miller went back to Berkeley in 1982 to take a faculty position. He was awarded an Alfred P. Sloan Research Fellowship to support his early research. During his time at Berkeley, Dr. Miller worked on a variety of neurobiological problems, ranging from LTP in the hippocampus to sensory processing in invertebrate systems. In 1994, Dr. Miller and five colleagues founded the *Journal of Computational Neuroscience*. Along with Dr. James Bower of CalTech, Dr. Miller also established the annual Computational Neuroscience (CNS) Meetings. Dr. Miller moved to Montana State University in 1997 to become the founding director of the Center for Computational Biology. Dr. Miller is on the advisory board of the Pittsburgh Supercomputer Center, and serves as one of 25 members on the President's Information Technology Advisory Committee (PITAC).

Dr. William Ditto is a researcher of nonlinear dynamics, and it is an exciting interdisciplinary field which encompasses all of the physical and natural sciences. The mandate of Professor Ditto's Applied Chaos Laboratory is the better understanding and manipulation of such nonlinear systems. Studies being performed in the Applied Chaos Lab include a wide range of computational and experimental projects both here at Tech and in collaborations with labs throughout North America. One exciting new area of recent interest is the control of chaos -- exploiting the sensitivity of chaotic systems to achieve control. Successes of the lab in this area include the control of: vibrating magnetoelastic ribbons, chaotically beating heart tissue and chaotically spiking brain tissue. Computational models of neural and cardiac excitable tissue and coupled nonlinear oscillators have been developed to enable us to understand basic temporal and spatiotemporal chaotic behaviors. Such models facilitate the development of novel methods for the detection, understanding and manipulation of chaos in biological and physical systems. Additional computational studies include utilization of noise, disorder, and chaos to enhance arrays of coupled nonlinear oscillators such Josephson Junctions and Duffing Oscillators. Electronic analog circuit experiments of such arrays are being planned to test the efficacy of nonlinear control and synchronization techniques.

Dr. Bruce Wheeler primary research interest lies in increasing our ability to observe the electrical activities of nerve cells, including fabrication of novel microelectrode arrays, their use in cell culture and in animals, and the development of automated computer data acquisition techniques to analyze neural activity. The last includes statistical pattern recognition techniques to interpret the neural firing patterns and to infer neural wiring from activity patterns. This work is done in collaboration with the Neuronal Pattern Analysis Group. A second focus is the

creation of precise patterns, with dimensions equal to those of individual cells, to guide nerve cell attachment and growth in culture. The group has adapted novel microlithographic techniques, including microcontact printing of proteins on cell culture surfaces. The goal is to synthesize neural networks in vitro and to couple them to microelectrode arrays, so that small populations of neurons can be assembled, stimulated, recorded, and optically identified. By attaching novel growth factors, selective growth (e.g. dendrites vs. axons) is to be achieved.

Dr. Andreas Offenhaeusser is presently at MPI for Polymer Research in Mainz, Germany. He received Diploma at Physics University of Ulm in 1985, earned his PhD from Biophysics University of Ulm in 1989 and in 2000, Habilitation from Physical Chemistry University of Tuebingen. In 1999, he became a Research Advisor in the Research Group for Spatio Temporal Function Materials, FRS, RIKEN, Japan and serves in that roll at the present. In 1994, he started as a Research Associate at Max-Planck-Institut für Polymerforschung, Mainz, Germany. From 1992-1994, he was at the Frontier Researcher, Lab. for Exotic Nano- Materials, Frontier Research Program, RIKEN, Japan and from 1990-1992, an Engineer at Robert Bosch GmbH, Reutlingen, Germany. His fields of major interest are bioelectronic devices and membrane biophysics. His professional society affiliations include Member of DPG (German Physical Society) and Member of DGfB (German Society for Biophysics).

Dr. Theodore W. Berger is Professor of Biomedical Engineering and Neurobiology, and Director of the Center for Neural Engineering, at the University of Southern California. Dr. Berger received his Ph.D. from Harvard University in 1976, for which he received the James McKeen Cattell Award from the New York Academy of Sciences. He conducted postdoctoral research at the University of California, Irvine from 1977-1978, and was an Alfred P. Sloan Foundation Fellow at The Salk Institute from 1978-1979. Dr. Berger joined the Departments of Neuroscience and Psychiatry at the University of Pittsburgh in 1979, being promoted through to the level of Full Professor in 1987. During that time, he received a McKnight Foundation Scholar Award, twice received an NIMH Research Scientist Development Award, and was elected a Fellow of the American Association for the Advancement of Science. Since 1992, he has been Professor of Biomedical Engineering and Neurobiology at the University of Southern California, and is a member of the Executive Committee of the Program in Neuroscience. While at USC, Dr. Berger has received an NIMH Senior Scientist Award, was awarded the Lockheed Senior Research Award in 1997, was elected a Fellow of the American Institute for Medical and Biological Engineering in 1998, and was recently appointed to the Division of Space Life Sciences Science Council of the Universities Space Research Association. Dr. Berger became Director of the Center for Neural Engineering in 1997, an organization which helps to unite the numerous USC faculty with cross-disciplinary interests in neuroscience, engineering, and the medicine.

Dr. Richard A. Andersen obtained the B.Sc. degree in Biochemistry from University of California, Davis, in 1973 and the Ph.D. in Physiology from University of California, San Francisco in 1979. He was a Postdoctoral Fellow at Johns Hopkins Medical School in Baltimore, MD in 1981, Assistant Professor (1981-1986) and Associate Professor (1986-1987) with the Salk Institute in La Jolla, CA, Associate Professor (1987-1990) and Professor (1990-1994) with the Department of Brain & Cognitive Sciences of the Massachusetts Institute of Technology, Cambridge, MA. In 1994 he joined the Biology Division of Caltech in Pasadena, CA, where he is the James G. Boswell Professor of Neuroscience. Since 1994, he is also Director of the Sloan Center for Theoretical Neurobiology at Caltech. Dr. Andersen was the recipient of the Spencer Award by Columbia University in 1994 and the McKnight Foundation Scholars

Award in 1983-1986, and was a Sloan Foundation Fellow between 1982-1986 and is a Fellow of the AAAS. He was a member of the International Neural Network Board of Directors between 1990-1994 and Director of the McDonnel/Pew Center for Cognitive Neuroscience at MIT between 1989-1994. Professor Andersen's research studies the neurobiological underpinnings to brain processes including the senses of sight, hearing and touch, the neural mechanisms of action, and the physical processes involved in learning and memory. He has published approximately 100 technical articles and one book.

Biological Information Processing and Systems Workshop
Other Biographical Sketches

Dr. Kamal Abdali received a Ph.D. in Computer Science from the University of Wisconsin, Madison, in 1974. He has been a computer science faculty member at New York University and the Rensselaer Polytechnic Institute, and has held adjunct appointments at the Oregon Graduate Institute and the University of Delaware. Prior to joining NSF, he was a principal scientist at the computer research lab in Tektronix, and led the symbolic computation research group there. His research has spanned the combinatory and lambda calculi, programming language semantics, and computer algebra language and systems design. His current interests include symbolic and algebraic computation, computer algebra systems, and automated theorem proving.

Dr. Bassem F. Armaly, Program Director from DOE in the Basic Energy Sciences.

Dr. Ruzena Bajcsy is a pioneering researcher in machine perception, robotics and artificial intelligence. She is a professor in both the Computer and Information Science Department and in the Mechanical Engineering and Applied Mechanics Department at the University of Pennsylvania, and is a member of the Neuroscience Institute in the School of Medicine. She is also director of the university's General Robotics and Active Sensory Perception Laboratory, which she founded in 1978. Dr. Bajcsy received her master's and Ph.D. degrees in electrical engineering from the Slovak Technical University in 1957 and 1967, respectively. She received a Ph.D. in computer science in 1972 from Stanford University, and since that time has been teaching and doing research at Penn's Department of Computer and Information Science. She began as an Assistant Professor and within 13 years, became Department Chair. Prior to the University of Pennsylvania, she taught during the 1950s and 1960s as an instructor and Assistant Professor in the Department of Mathematics and Department of Computer Science at Slovak Technical University in Bratislava. She has served as advisor to more than 20 Ph.D. recipients.

Dr. John Blair, Principal with JBX Technologies, Inc., has his B.S., M.S., and Sc.D. from MIT in Electrical Engineering. His fields of expertise include sensors and sensor based systems; solid state electronics, semiconductors, and devices; and materials engineering. He is the former Director of Research with the Raytheon Company for twenty-eight years, and a former MIT professor. His awards and honors include the Citation for Patriotic Civilian Service, Secretary of the Army; a Ford Foundation Post-doctoral Fellow; and a Senior Life Member of IEEE.

Dr. Tom Boland, Assistant Professor from Clemson University in the Department of Bioengineering. He received his Ph.D. in Chemical Engineering at University of Washington. He is interested in Atomic Force Microscopy, Self-Assembled Monolayers, Lagmuir-Blodgett

films and Biointerfaces. His research areas include Protein Adsorption to Model Surfaces, Cell Adhesion to Protein Films, and Design of Supracellular Assemblies.

Dr. Eugene N. Bruce, Program Officer, Integrative Activities from NSF in the BIO/IBN.

Dr. Bruce Cohen is an Assistant Professor of Neurosciences at the University of California, Riverside, in the Division of Biomedical Sciences. He received his PhD in 1985 from the State University of New York at Albany in Neurobiology. Prior to his appointment at U.C., he was a Research Fellow with Dr. Henry A. Lester, Division of Biology, at the California Institute of Technology in Pasadena, where he was working on "Location of ion-selectivity filter of ACh channel using site-directed mutagenesis". As a postgraduate researcher with Dr. Gordon L. Fain, Jules Stein Eye Institute, University of California at Los Angeles Medical School, he conducted the "Patch-clamp study of neurotransmitter-activated channels in isolated ganglion cells from the goldfish retina". In 1997, he received the UC Regent's Faculty Fellowship award, and in 1990, he attended the Gordon Conference on Ion Channels. Dr. Cohen's research interests include structure-function of ligand gated channels, cloning new ion channels, ion channel diseases, and ion channel pharmacology.

Dr. Darren M. Dawson received an Associate Degree in Mathematics from Macon Junior College in 1982 and a B.S. Degree in Electrical Engineering from the Georgia Institute of Technology in 1984. He worked for Westinghouse as a control engineer from 1985 to 1987. In 1987, he returned to the Georgia Institute of Technology where he received a Ph.D. Degree in Electrical Engineering in March 1990. In July 1990, he joined the Electrical and Computer Engineering Department and the Center for Advanced Manufacturing (CAM) at Clemson University where he currently holds the position of Professor. Under the CAM director's supervision, he currently leads the Robotics and Mechatronics Laboratory, which is jointly operated by the Electrical and Mechanical Engineering departments. Dr. Dawson has served the control and robotics community in the following capacities: Present Associate Editor, IEEE Transactions on Control System Technology, Past Associate Editor of Automatica, The International Federation of Automatic Control (IFAC) Journal, served on the International Program Committee for the Symposium on Implicit and Nonlinear Systems (1992), the International Program Committee for the 3rd IEEE Mediterranean Symposium on New Directions in Control and Automation, the International Program Committee for the 4th IEEE Mediterranean Symposium on New Directions in Control and Automation, and is presently serving on the International Program Committee for the 7th IEEE Conference on Control Application (1998). Professor Dawson's research interests include: i) Nonlinear Control Techniques for Mechatronic Systems such as Electric Machinery, Robotic Manipulator Systems, Overhead Cranes, Rapid Isothermal Processing of Electronic Materials, Magnetic Bearings, and Mechanical Friction, ii) Boundary Control of Distributed Parameter Systems such as Paper Handling and Textile Machines, Flexible Beams/Robots/Rotors, and Cable Structures, iii) Robust and Adaptive Control of Uncertain Nonlinear Systems, iv) Partial State Feedback and Output Feedback Control Techniques and v) Realtime Hardware and Software Systems for Control Implementation.

Dr. Alison Deckhut joined the Division of Allergy Immunology and Transplantation at the National Institute of Allergy, Immunology and Infectious Disease in December 1999, serving as a Program Officer in the Basic Immunology Branch. Dr. Deckhut received her Ph.D. degree in immunology from Pennsylvania State University College of Medicine in 1991. She completed her postdoctoral work at St. Jude's Children's Research Hospital and at Johns Hopkins University

Medical School. She was appointed Senior Staff Fellow at the National Institute of Neurological Disorders and Stroke in 1997. Her research experience includes work on TCR-MHC-superantigen interactions in T cell activation, TCR usage by influenza-specific T cells, CD8 T cells specific for the SV40 Tumor (T) antigen, CD8 T cell responses to tumor-vaccinated renal cell carcinoma patients, and analyses of the cell-mediated immune responses to JC virus in humans. As a program officer, Dr. Deckhut manages programs related to bioengineering, biotechnology, computer modeling of immune function, basic aspects of antigen processing, lymphocyte memory development, and B cell function.

Dr. Michael M. Domach, Program Director from NSF in the ENG/BES.

Dr. R. Larry Dooley is Professor and Chair, Bioengineering Department at Clemson University. He obtained his B.S. in Mechanical Engineering (1969) at Virginia Polytechnic Institute & State University, an M.S. in Bioengineering (1973) at Clemson University, and a Ph.D. in Bioengineering at Clemson University. He is interested in Scientific visualization, Computation modeling, Advanced manufacturing techniques, and Microstructural engineering of materials. The current areas of research in Dr. Dooley's lab include: Stereolitography Research Testbeds, An Expert System Orthopedic Workstation, Advanced Imaging and Documentation Techniques, and Custom Implant Technology.

Dr. William Franklin is the Program Director from NSF/CISE/C-CR in Numeric, Symbolic, & Geometric Computation.

Dr. Doug Gage manages the SDR and MARS programs. Prior to joining DARPA in 2000, he was with the Space and Naval Warfare System Center San Diego and its predecessor organizations NRaD, NOSC, and NELC, where he managed and/or participated in a number of programs principally in the areas of robotic unmanned ground vehicles and sensor networks. Dr. Gage holds a B.S. degree from Caltech, and M.S. and Ph.D. degrees (all in physics) from Arizona State University. He is a member of IEEE, AAAI, and AUVSI.

Dr. Roger P. Gaumond received a B.S. from the Mass. Inst. of Technology in Electrical Engineering in 1968, a M. Eng. from Cal Poly San Luis Obispo, a CA in Electrical Engineering in 1974, and his D.Sc. from Washington University, St Louis, MO in Electrical Engineering in 1980. Dr. Gaumond is presently an Associate Professor in the Bioengineering Program at Pennsylvania State University. He is conducting research on the magnetic stimulation of nerve fibers, nerve fiber response characterization, evoked potential, electrocardiographic signal analysis, and studies of inductive energy transfer systems for artificial organs. He teaches courses in biomedical instrumentation, laboratory computers, and physiological systems analysis and, he is in charge of the undergraduate Minor in Bioengineering.

Dr. Robert Geist, is a Professor in the Computer Science Department at Clemson University. He obtained his B.A. in Mathematics at Duke University (1970), a M.S. in Mathematics at University of Notre Dame (1973) and Ph.D. in Mathematics at the University of Notre Dame (1974). He also obtained a M.A. in Computer Science at Duke University (1980). His research is focused on Systems modeling, Performance evaluation, Reliability modeling, and Graphics.

Dr. Richard J. Goldstein is Regents' and James J. Ryan Professor of Mechanical Engineering at the University of Minnesota, a member of the U.S. National Academy of Engineering, and currently President of the International Center for Heat and Mass Transfer. He is a Past

President of the American Society of Mechanical Engineers and of the Assembly for International Heat Transfer Conferences. At the University of Minnesota, he teaches and does research related to fluid mechanics, heat transfer, and energy systems.

Dr. Doris R. Helms is the Provost and Vice President for Academic Affairs at Clemson University. She received her PhD from the University of Georgia, Athens, in 1973 (Zoology—concentration, molecular biology). Her dissertation title was *Nuclear and Cytoplasmic Ribonucleoprotein Particles Isolated from the Salivary Glands of* Rhynchosciara hollaenderi under director Ellen Mattingly. Dr. Helms' accomplishments at Clemson include developing a University academic "roadmap" for moving Clemson into the "Top Twenty" among public universities (Clemson is currently ranked 39th); coordinating the development of five-year strategic academic and business plans for all colleges and divisions of Academic Affairs; assisting the University President with development and implementation of a collaborative administrative evaluation network and academic organizational restructuring; developing and implementing the Faculty Activity System (FAS)—a campus wide electronic workload analysis system used to collect information for annual review, management, and accountability; implementing a Post-Tenure Review program; implementing the Academic Deans Evaluation Program; supporting the establishment of the University Ombudsman Office, Student Academic Assistance Center, and Office of Teaching Effectiveness and Innovation; establishing the College of Sciences Teaching Assistant Training Program; establishing TEAMS (Tools for Enrichment and Advancement in Mathematics and Science), a mentoring program to improve retention of minority students; establishing the Educational Information Technology Laboratory (EITL), a multimedia technology laboratory; establishing a unique instructional program that developed into a thriving department, the Biology Program (now the Department of Agricultural Instruction and Biology Education); developing a statewide support network for biology teachers; developing and implementing plans for a statewide network of science centers to serve K-12 teachers and schools; and introducing investigative laboratories into standard biological sciences curriculum. Dr. Helms' professional interests include the areas of Administration, Instruction, and Developmental Biology (genomics, molecular control mechanisms in differentiation, and biodiversity).

Dr. John Hetling is an assistant professor in the Department of Bioengineering at the University of Illinois, Chiacago. He received his B.S. in Biology at Bates College (1989) and his Ph.D. in Bioengineering at the University of Illinois (1997). After graduating from Bates College John Hetling worked for two years in the neuroelectrophysiology laboratory of Dr. Patsy Dickinson at Bowdoin College, studying rhythmic motor pattern generation. His interests can be summarized as dealing with the extraction of information form complex or inaccessible biological systems, specifically studying phototransduction in living animals, and large pattern-generating neural networks. Some of the current projects include 1) Development of a retinal neural prosthetic device, 2) Convergent mapping of potentiometer probe image data into a binary, 2-D data structure suitable for extended dependency analysis and 3) Development of micro fabricated linear array electrode to enable stimultaneous multi-depth recording in the retina; data will be used to perform current-source density analysis of prosthesis-mediated physiological responses.

Dr. Lila Kari is an Associate Professor and Canada Research Chair in Biocomputing from the University of Western Ontario in the Department of Computer Science. Her achievements include being the winner of the 1991 Nevanlinna Prize for Finland's best doctoral dissertation in the mathematical sciences; widely recognized for pioneering research into the information processing capabilities of unicellular organisms; numerous papers and journal articles on the

potential of biological computing; and being an invited speaker at numerous conferences in disciplines as varied as physics, mathematics, bionomics biology, and unconventional computing. Dr. Kari's research involves solving language problems to utilize the computational potential of living organisms in order to tap into the biological process as a computational tool. And from PC to DNA--can DNA compute? She is exploring the possibility of using the deoxyribonucleic acid that exists in every cellular organism to solve complex computation problems at many times the speed of electronic digital computers and harness the computational abilities of living organisms. The practical use of organisms to process information - just as cells "compute" data as part of their usual function - opens up as-yet unimagined horizons for a DNA computer that could be thousands to millions of times faster, trillions of times smaller and thousands of times more energy efficient than today's electronic computers. Dr. Kari's research covers three related areas: biomolecular computation, or how to employ biomolecules to perform computations; biological computation, or how biological systems process information; and bioinformatics, or how to apply data modeling and algorithmic techniques to biological problems. The result of this research will further the understanding of the workings of the cell to determine its unique algorithms and computational elements, and allow the cell's enormous capability to be explored in a controlled fashion. The work falls into three broad goals: understanding the meaning of the sequences and interconnections of the human genome in an effort to better understand DNA and genetic code; measuring the information content and complexity of the gene languages of various organisms; and the development of a computational model of cellular genetics, along with an accurate model of gene function and expression in living organisms.

Dr. Thomas M. Keinath serves as dean of the College of Engineering and Science at Clemson University. He assumed this position on July 1, 1992, after serving as Department Head of Environmental Engineering and Science at Clemson since 1976. Dr. Keinath's major teaching and research interests are in the modeling and control of water and wastewater treatment facilities and, physicochemical methods of treating waters, wastewaters and groundwaters. The majority of his research focuses on adsorption/exchange processes on soils and synthetic materials, and on secondary clarification. Dr. Keinath has directed the research of 63 M.S. students, 16 Ph.D. students and 8 postdoctoral students. He has been an active member of major national and international professional organizations concerned with water quality control. Dr. Keinath presently serves as the immediate past president of the International Association of Water Quality and is a member of its Executive Committee and Governing Board. He also served as chair of the Program Committee of the Water Environment Federation and is a past president of the Association of Environmental Engineering and Science Professors. He served the American Society of Civil Engineers as chair of its Clarifier Research Technical Committee.

Dr. Joanne K. Kelleher is Research Professor in the Department of Physiology George Washington University Medical School. She studied basic metabolic pathways in mammalian systems. Her laboratory focuses on carbohydrate, lipid and amino acid metabolism in normal conditions and metabolic diseases, especially Diabetes. The goal of her research is a quantitative understanding of metabolic flux. To accomplish this goal she uses isotopic methods for the tracking of metabolic fluxes and modeling approaches to analyze isotopic data. She has developed the Isotopomer Spectral Analysis method for determining the enrichment of precursors in biosynthesis, allowing improved estimates of rates of synthesis. With the completion of the human genome project, a major challenge is to establish links between metabolic activity and gene expression (mRNA profiles) and between metabolic activity and allelic variations or mutations. Her laboratory is interested in experimental methods and

bioinformatics tools to establish these links. Her research is funded by the NIH and American Diabetes Association. She has held a NIH Special Emphasis Career Award and a NSF POWRE award. At present she is on sabbatical at MIT in the Department of Chemical Engineering.

Dr. Henry Kelly is the President of the Federation of American Scientists, a non-profit science and technology policy organization founded in 1945. He was Assistant Director for Technology at the White House Office of Science and Technology Policy from 1993 to 2000 where he supported the administration's efforts in information technology (President's Information Technology Advisory Committee, Next Generation Internet, Information Technology Research Initiative, Partnership for a New Generation of Vehicles, Bio-energy initiative, and other work), Assistant Director of the Solar Energy Research Institute (now NREL), and Senior Associate and Program Manager at the Congressional Office of Technology Assessment. He also worked on strategic arms control at the Arms Control and Disarmament Agency. Kelly has a PhD in Physics from Harvard University, a BA from Cornell University, and is a Fellow of the American Physical Society. He is the author of many books and publications on science and technology policy, energy and the environment, learning technology, and information policy.

Dr. Sri Kumar is on loan to DARPA from NIST where he is the Senior Technical Advisor, Advanced Network Technologies Division. Prior to Dr. Kumar's assignment to NIST, he was a Faculty member and Director of the Information Technology Program at Northwestern University. Dr. Kumar has also held the position of Assistant Professor at Rensselear Polytechnic Institute as well as the State University of New York, Buffalo.

Dr. Robert Latour received his Ph.D. in Bioengineering at the University of Pennsylvania. He is interested in implant biomaterials, biomechanics, computational-chemistry based biomolecular modeling, and the thermodynamics of protein-surface and protein-cell interactions. His current areas of research include orthopedic device design, analysis, and evaluation; the molecular modeling of protein-surface interactions; and protein-surface binding affinity studies.

Dr. Larry Lok, Research Fellow from the Molecular Sciences Institute.

Dr. Arun Majumdar is a Professor and the Vice-Chairman (Instructions) in the Department of Mechanical Engineering, University of California, Berkeley. He completed his B.Tech. in ME from the Indian Institute of Technology, Bombay in 1985 and his Ph.D. in ME from UC Berkeley in 1989. Subsequently, he was at Arizona State Univ. (1989-92) and UC Santa Barbara (1992-96) as a faculty in Mechanical Engineering. He is a recipient of the NSF Young Investigator Award, the ASME Melville Medal, and the ASME Best Paper Award from the Heat Transfer Division. He is currently serving as an associate editor for the ASME Journal of Heat Transfer and the Int. Journal of Heat and Mass Transfer, and the co-editor-in-chief of Microscale Thermophysical Engineering. He also serves as a member of the Council on Energy Engineering Research for the Department of Energy. He is interested in Nanoscale Diagnostics (Scanning Probe Microscopy), Energy Conversion and Transport in Nanostructures, Optomechanical Microdevices, and Nano-Biomolecular Engineering.

Dr. Peter Molnar is a Post Doctoral Fellow at Clemson University in the Department of Bioengineering. Dr. Molar received his B.S. (Physics, Biophysics) from the Eötvös Lorand University of Sciences Budapest, Hungary in 1989 and his Ph.D. (Biophysics) from the Eötvös Lorand University of Sciences Budapest, Hungary in 1992. He is an electrophysiologist devoted to the study of the central nervous system, normal and pathological behavior of neural networks

and ion channels, synaptic plasticity, neurodegenerative diseases, memory and learning processes. Before coming to Clemson, he was a Research Associate at Duke University Medical Center in the Department of. Pharmacology. He was also a Research Scientist, Project manager at Chinoin Co. Ltd., CNS Pharmacology in Budapest, Hungary and was a Research Scientist at Richter Gedeon Co. Ltd. in the Dept. of Biochemistry.

Dr. Sacha Nelson is an Associate Professor in the department of Biology and the Center for Complex Systems at Brandeis University and is the current chair of the Brandeis Graduate Program in Neuroscience. He received BA and Sc.B. degrees from Brown University in 1983 and M.D. and Ph.D. degrees from UCSD in 1991, after thesis work in the laboratory of Simon LeVay at the Salk Institute. He went on to postdoctoral training with Mriganka Sur in the department of Brain and Cognitive Science at MIT before joining the Brandeis faculty in 1994. Nelson's work focuses on biophysical and systems-level analysis of synaptic plasticity in the neocortex and has been supported by grants from NEI, NIMH, NSF, the Sloan Foundation, and the Human Frontiers of Science Program.

Dr. Margaret A. Palmer, Professor, Department of Biology at the University of Maryland, and Program Director, Ecology from NSF in the Division of Environmental Biology. Dr. Palmer's research interests include Aquatic Ecology focusing on Invertebrate Community Ecology; Restoration Ecology; Patch Dynamics & Landscape Ecology. The broad objective of her research is to understand what controls the establishment and survival of stream invertebrates. She specifically focuses on the relative importance of geomorphic/hydrodynamic factors in predicting invertebrate colonization of new habitats, post-recruitment survival, biodiversity and restoration of ecological processes. Her work also addresses the role of spatial habitat configuration in invertebrate population and community dynamics. Dr. Palmer has a diverse research group in her lab with broad training in the ecology freshwater systems, fluid dynamics, and hydrology. The research includes field experimentation and laboratory experiments performed on the main campus as well as in her nearby recirculating flume laboratory.

Dr. James K. Peterson is an Associate Professor from Clemson University in the Department of Mathematical Sciences. He earned his MS in Mathematics at Colorado State University in 1977, with his thesis entitled "The Burnside Conjecture in Finite Groups". Dr. Peterson has a PhD in Mathematics from Colorado State University, 1980, and wrote his dissertation on "Degree Theoretic Methods in Optimal Control". His University experience consists of 5 years at Michigan Technological University (1980 - 1985) and Clemson University (1990 - 2001). In between, the he worked at primarily Aerospace companies (Aerospace Corporation on spaced shuttle optimization tasks, Lear-Siegler / Smith Industries on algorithm development for optimal route planning for large strategic missions) and software development at a startup company called KDi Industries. Exposure to soft computing strategies such as neural networks began when he was the lead designer for strategic missions software for large scale management purposes (1987-1989) and has continued since then. Dr. Peterson has had previous NSF support for the development of software and algorithms for control using neural network technologies. In addition, he has been trained in cross-disciplinary work on computer science and biology by McDonnell Foundation. This has led to the development of software codes for Beowulf cluster hardware platforms which focus on asynchronous computation using a variety of computational objects. The biological, hardware and software portions of this research are currently being funded through NSF via an SGER. Current work includes algorithm design for parsing the output of an excitable nerve cell/ silicon hybrid that is joint with colleagues in Bioengineering at Clemson University.

Dr. Christian Przirembel obtained his Ph.D., in Mechanical and Aerospace Engineering, at Rutgers University in 1967. At present, he is Professor of Mechanical Engineering (1981-present). From 1981-1994, he was the head of Mechanical Engineering and, from 1994-2001, he was the Associate Dean of Engineering for Research and Graduate Studies. He is interested in Subsonic and supersonic separated flows, resonance tubes and flow measurements.

Dr. Shankar Sastry was the Director of the Electronics Research Laboratory and Professor of Electrical Engineering and Computer Science at the University of California, Berkeley. He holds a M.S. and Ph.D. in Electrical Engineering and Computer Science, as well as a M.A. in Mathematics, all from UC, Berkeley.

Dr. Y. T. Shah is senior vice provost for research and graduate studies and chief research officer. Shah is currently a Distinguished Professor and dean of the College of Engineering at Drexel University in Philadelphia, Pa. Dr. Shah is responsible for stimulating, developing, marketing, and coordinating Clemson's research programs and for helping the state recruit and support high technology and manufacturing industries. Shah's four degrees in chemical engineering include a bachelor's degree from the University of Michigan and three advanced degrees from the Massachusetts Institute of Technology. His field of specialization is energy, environmental, and waste conversion technologies. After serving on the faculty of the University of Pittsburgh from 1969 until 1987, he was dean of engineering and science at the University of Tulsa for four years. He moved to Drexel in 1991. He has worked with industries ranging from Fluor Daniel to Texaco. Dr. Shah was selected for the Clemson post after a national search that lasted seven months and attracted 95 applicants.

Dr. Carol Soderlund is an Associate Professor at Clemson University in the Computer Science Department.

Dr. Sylvia Spengler, with a Ph.D. in physics/biophysics from UC Berkeley, is the Program Officer for Biological Databases and Informatics at NSF. She is an IPA from Lawrence Berkeley National Laboratory, where she is the co-Head of the Center for Bioinformatics and Computational Genomics. She was a founding member of the Program in Mathematics and Molecular Biology at Berkeley, now at FSU, and was its Director for two years. Her research interests include: DNA structure, sequence analysis, and phyloinformatics, as well as the ethical and social impacts of technologies.

Dr. Pradip Srimani received his Ph. D. in Computer Science at the University of Calcutta, India. As of August 2000 he has been a Professor & Chair at Clemson University, Clemson, South Carolina. His research interests are, Distributed Systems, Mobile Computing, Parallel Algorithms, Interconnection Networks, Data Structures, Fault-Tolerant Computing, and Graph Theory & Applications.

Dr. Mark L. Swinson is the deputy director of DARPA's Information Technology Office. He also recently served as the program manager for the Embedded Systems Program, the Mobile Autonomous Robot Software Program, and the Software for Distributed Robotics Program. Dr. Swinson is recognized internationally as an expert in mobile robot technology, especially for military applications. A recently retired Army Colonel, he was the Army's senior roboticist. His research interests include embedded software, intelligent mechatronic systems, distributed processing, domain-specific languages, and machine learning for robot programming. He is a

member of the American Association for Artificial Intelligence, American Society of Mechanical Engineers, American Society for Engineering Education, Association for Unmanned Vehicle Systems International, and Institute of Electrical and Electronics Engineers. He received his BS in engineering from the US Military Academy at West Point, his MS in mechanical engineering from the University of Wisconsin, and his Ph.D. in robot control systems from the University in Florida. He can be contacted at the Defense Advanced Research Projects Agency, Information Technology Office, 3701 Fairfax Dr., Arlington, VA 22203-1714; mswinson@darpa.mil; www.darpa.mil/ito/Personnel/mswinson.html.

Dr. Nitish Thakor, is professor of Biomedical Engineering at Johns Hopkins University School of Medicine. He obtained his B.S. in Electrical Engineering, at the Indian Institute of Technology, Bombay (1969-1974), M.S. in Biomedical Engineering, at the University of Wisconsin, Madison (1977-1978) and a Ph.D. in Electrical and Computer Eng. at the University of Wisconsin, Madison (1979-1981). His laboratory conducts research on Biomedical Instrumentation, Signal Processing, and Computer Applications. The principal focus is on cardiovascular and neurological patient monitoring instrumentation. Dr. Thakor has also collaborated on other applications (rehabilitation and robotics, molecular engineering and technologies). The research is often carried out in collaboration with clinical colleagues and is usually sponsored by Federal agencies such as the National Institutes of Health and the National Science Foundation, foundations and medical device industry.

Dr. Eberhard Voit, Professor from Medical Univeristy of SC in the Biometry and Epidemiology. He obtained his B.S. at the Universitat zu Koln (1973) in Natural Sciences and Mathematics (1975). In 1976, he received a M.S. in Biology at Universitat su Koln and in 1977 he obtained a M.S. in Mathematics at the same University. In 1981 he obtained his Ph.D. in Devel./Theor. Biology at the Universitat zu Koln. He is interested in organizationally complex systems, metabolic pathways, canonical modeling, S-systems, and S-distributions.

Dr. James T. Woo is President and Chief Executive Officer of InterScience, Inc., a small technology-based research and development company he founded in 1980 headquartered in Troy, New York. The mission of the company is to develop and integrate advanced technologies for new applications. He received his baccalaureate degree in Engineering Science from the University of Portland in 1959. Following graduation, he did graduate work at the Stevens Institute of Technology and Columbia University while working as a Radiation Physicist at the Columbia Presbyterian Hospital in New York City. He then became interested in the then emerging field of controlled thermonuclear fusion power and enrolled at Massachusetts Institute of Technology to pursue graduate education in this field from which he received his Doctorate in Nuclear Engineering in 1966. His early professional career was engaged in conducting basic research in plasma physics at Mt. Auburn Research Associates (1966-1968) and development of laser, RF and particle beam heating technologies for thermonuclear fusion by both magnetic and inertial confinement at the United Technologies Research Center (1969-1975). He then moved to an academic milieu and taught in the Department of Nuclear Engineering at MIT as a visiting faculty member (1975-1977) and in the Department of Electrical Engineering at the Rensselaer Polytechnic Institute (1977-1981). While he was on the faculty of RPI, he came to recognize the need to bridge the gap between basic research and practical applications. Believing this gap could best be closed by technology entrepreneurship, he founded InterScience, Inc. to pursue such opportunities. Under his leadership, the company has expanded into the development and applications of a broad range of advanced technologies with current emphasis in electro-optics, micro electro-mechanical systems (MEMS), plasma processing of materials, signal processing,

and optical based instruments for industrial inspection and medical diagnostics. The company pursues commercialization of the technologies through licensing, strategic partnering and spin-off companies. The company is actively engaged in product development for a number of commercial customers as well as conducting federal government sponsored research. He is a co-founder of Plasma Pyrolysis Systems, Inc., a related company dedicated to the application of plasma for material processing. In directing the growth of the company, Dr. Woo became an activist in advancing the interest of small technology enterprises. He was elected a delegate from New York to the 1995 White House Conference on Small Business and subsequently elected by the other delegates as the Technology co-Chair for Region II. In this role, along with many of his counterparts from other regions, he spearheaded the formation of the Small Business Technology Coalition with the mission to educate the public, the financial community, and the Congress on the importance of nurturing the growth of small technology enterprises, as well as assisting technology entrepreneurs in networking to grow their business. Dr. Woo served as the Founding Chairman of the SBTC for two years from 1996 through 1998 and the organization now has several hundred members nationwide with headquarters in Washington, DC. From 1998 to 2001, he had served as a member of the Council on Energy Engineering Research for the U. S. Department of Energy's Basic Energy Research Program.

Dr. Alan Yuille received his BA in Mathematics at the University of Cambridge in 1976. He completed his PhD in Theoretical Physics at Cambridge in 1980 and worked as a postdoc in Physics at the University of Texas at Austin and the Institute for Theoretical Physics at Santa Barbara. From 1982-86 he worked at the Artificial Intelligence Laboratory at MIT before joining the Division of Applied Sciences at Harvard from 1986-1995 rising to the rank of Associate Professor of Computer Science. In 1995 he joined the Smith-Kettlewell Eye Research Institute in San Francisco. His research interests are in mathematical modeling of artificial and biological vision. He has over one hundred peer-reviewed publications in vision, neural networks, and physics. He has co-authored two books -- "Data Fusion for Sensory Information Processing Systems" J.J. Clark and A.L. Yuille, and "Two- and Three- Dimensional Patterns of the Face" P.W. Hallinan, G.G. Gordon, A.L. Yuille, P.J. Giblin and D.B. Mumford -- and edited a book "Active Vision" with A. Blake.